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CORRIGENDUM

Page 171, line 2, *for* Archibalde *read* Archibald.

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PARAPLEGIA AND CAUDA EQUINA SYMPTOMS IN LYMPHOGRANULOMATOSIS MALIGNA (HODGKIN'S DISEASE)

By F. PARKES WEBER

AMONGST the rarer clinical and pathological features of lymphogranulomatosis maligna, one of the least known ones is the occurrence of cauda equina symptoms or paraplegia. O. Naegeli and Kurt Ziegler both refer to cases, but I can find very few definite accounts in the literature. Dr. S. A. Kinnier Wilson kindly tells me that he has had an as yet unpublished fatal case in a young man. There was no post-mortem examination, but the symptoms observed during life made the diagnosis practically certain. Similarly, Dr. H. Letheby Tidy was good enough to tell me of a soldier admitted during the war to a fever hospital in France, with a diagnosis of typhoid fever, based on pyrexia and splenic enlargement. But the patient was found to have Hodgkin's disease. He had masses of glands in the neck and pains in the legs; and, under observation, he developed paraplegia. The final history was not known. The following case (Case I) is that of a young man, aged 21 years, who had suffered from typical lymphogranulomatosis maligna (Hodgkin's disease) for some years before the onset of paraplegia and his death. The post-mortem examination showed the paraplegia to be caused by lymphogranulomatous growths within the vertebral canal.

Case I. The patient (H. W.), then aged 19 years, was admitted to hospital under my care on September 8, 1919. At that time he had a few slightly enlarged glands on both sides of the neck and deep jaundice. The jaundice, which was not accompanied by 'acholic' faeces, was possibly due to previous arsenical medication, and it gradually passed off in the course of some weeks. Several months previously, on December 7, 1918, my surgical colleague, Mr. A. Compton, had excised considerably enlarged glands on the right side of the neck, and a microscopical diagnosis of Hodgkin's disease had been made. The disease had previously been for a time accompanied by rather high pyrexia. There was still frequently moderate fever, up to about 100° F. in the afternoons. Röntgen-ray examination of the thorax (September 1919) showed hilus thickening and a few small hilus glands on both sides (Dr. J. Metcalfe). From September 19, 1919, there was practically no fever, and on October 24, 1919, Mr. A. Compton, under local anaesthesia, excised the remaining enlarged glands from the right side of the neck. The excised glands macroscopically showed no necrotic or caseous foci; they were not abnormally adherent to each other, and microscopical sections gave the picture of lymphogranulomatosis maligna (Hodgkin's disease), with the mononuclear (endothelioid) and polynuclear giant-cells characteristic of the disease.

In November 1919 there was often slight fever in the afternoons, and on

[Q. J. M., Oct., 1923.]

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November 12 Mr. A. Compton excised the enlarged glands from the left side of the neck. The patient left the hospital on November 22, 1919.

After leaving the hospital there was again progressive glandular enlargement on the right side of the neck. But in 1920, under Röntgen-ray treatment in the out-patient department, these glands diminished in size. The Röntgen-ray treatment was discontinued in October 1920.

In February 1921 the patient commenced to suffer from lumbar pain. This lasted for six weeks, and then, at the commencement of April 1921, he complained of pain in the right thigh, which was still present when he was readmitted to hospital under my care on April 28, 1921.

On readmission I could make out no definite enlargement of superficial lymph-glands, nor anything abnormal in the spleen, liver, or other viscera. He was very pale, and a blood-count (April 29) gave 2,120,000 red cells and 4,400 white cells to the cubic millimetre of blood. The patient was treated firstly with Fowler's solution and then with arsacetin. By May 1921, apart from the pain previously complained of, more or less actual paraplegia had developed, and early in July the plantar reflexes on both sides were noted to be of the extensor type (Babinski's sign). In May, also, considerable pyrexia of hectic type commenced, and it continued in more or less degree till a few days before the patient's death on December 6, 1921.

A few other observations made before the patient's death must here be noted. A Pirquet's cuti-reaction for tuberculosis on October 4 gave a negative result. Enlargement of the spleen and liver was made out in August, when there was also definite hypo-aesthesia in the lower extremities and the back of the pelvis, and a slight bed-sore began to develop. Ophthalmoscopic examination in July showed nothing abnormal. In November there was slight ascites, and an opalescent serous effusion had to be drawn off from the right pleura; the ascites later on disappeared; the urine was free from albumin and sugar. At the commencement of November considerable fresh glandular enlargement (relatively soft and rapidly growing nodules) was noted on both sides of the neck.

In regard to blood-counts the most noticeable feature was a progressive leucopenia. On July 7 there were 3,060,000 red cells and 3,500 white cells to the cubic millimetre of blood; a differential count of the white cells gave 57 per cent. polymorphonuclear neutrophils, 38.6 per cent. lymphocytes, and 4.4 per cent. transitionals and large mononuclears; no eosinophils or mast-cells were observed amongst the cells counted. On October 20 the red cells had risen to 4,140,000, whereas the white cells had fallen to 2,800; haemoglobin, 58 per cent. On November 3 the red cells were 3,800,000; the white cells had fallen to 1,900; haemoglobin, 45 per cent. Leucopenia in advanced lymphogranulomatosis maligna is by no means uncommon, as I, amongst others, have elsewhere pointed out. In regard to other features of the blood-counts in this case, the possible influence on the red cells and polymorphonuclears of prolonged Röntgen-ray treatment should not be forgotten.

The *necropsy*¹ (December 6, about six hours after death) showed masses of enlarged retroperitoneal glands and other enlarged abdominal lymphatic glands—typical of lymphogranulomatosis maligna. Some pleural effusion was present on both sides. There was no evidence of tuberculosis in the lungs or elsewhere. The moderately enlarged spleen weighed 17 ounces and contained yellowish nodules. The liver weighed 70 ounces and showed fatty infiltration. There was considerable fibrosis of the lymphatic glands about the vertebral column; but quite distinct from that was a remarkable (lymphogranulomatous) thickening of the periosteum on both outer sides of the vertebral centra about the region of the diaphragm. Microscopic examination of this periosteal growth proved it to be of true lymphogranulomatous nature, containing endothelioid cells and

¹ In regard to this I have to thank Dr. Elsener, one of the house physicians, and I have likewise to thank Dr. Lang, the other house physician, for some blood-counts.

lymphogranulomatous giant-cells. After opening the vertebral canal lymphogranulomatous growth—having exactly the same microscopic structure as that of the above-mentioned (outer) periosteal growth—was found attached to the outside of the dura mater over the end of the spinal cord and farther down over the cauda equina, thus accounting for the paraplegic symptoms present during life. I have little doubt that this lymphogranulomatous growth situated between the spinal dura mater and the bony walls of the vertebral canal was altogether analogous to the above-mentioned periosteal growth outside the vertebral centra; in fact, the loose connective and fatty tissue between the spinal dura mater and the bone practically corresponds to periosteum (from the developmental point of view).

O. Naegeli (1), who refers to periosteal growths or infiltrations as atypical findings in cases of lymphogranulomatosis maligna, says that they are generally not discovered till the post-mortem examination.

In regard to the fibrosis of the enlarged lymphatic glands near the vertebral column, I may mention that in a hospital patient of mine (Mrs. M. H.), aged 45 years, who died from lymphogranulomatosis maligna in January 1915, the abdominal aorta near its bifurcation was found partially embedded in a hard whitish growth, doubtless formed by the merging together of lymphogranulomatous para-aortic glands, so as to form a firm fibroid lymphogranulomatous mass. There can be no doubt that occasionally, though rarely, in cases of lymphogranulomatosis maligna the lymphogranulomatous process extends beyond the capsules of the lymphatic glands so as to invade the peri-glandular tissue, thus forming dense tumour-like 'matted' masses. O. Naegeli (1) writes that occasionally in some places the tissue neighbouring lymphogranulomatous glands may undergo tumour-like lymphogranulomatous infiltration, as in a case which was formerly supposed to be one of lymphosarcoma by Dietrich. It is possible that, in the case of the patient Mrs. M. H., Röntgen-ray treatment of the intra-abdominal portion of the disease during life helped to cause matting of the glands together, and thus to produce the curious fibroid mass found at the post-mortem examination, adherent to and partly enclosing the aorta at its bifurcation. Microscopic sections of the hard 'growth' in question (kindly made by Dr. H. Schmidt) showed only hyaline fibroid tissue containing the remains of lymphadenoid tissue to indicate its lymphogranulomatous origin, and containing also strands of adipose tissue, nerves, and a nerve-ganglion with many typical large ganglion-cells.

Case II. Hermann Eichhorst (2). The patient was a boy, aged 17 years, with great chronic enlargement of superficial lymphatic glands. Four months before his death there was considerable increase in the number of his white blood-cells. At the commencement of November 1897 the red cells were 3,600,000 and the white cells (mostly polymorphonuclear neutrophils) 41,650 to the c.mm. of blood. On January 7, 1898, the red cells were 3,300,000 and the white cells 45,000 to the c.mm. of blood. The patient died on February 2, 1898. During the last two or three weeks of life there had been signs of involvement of the spinal cord, with almost complete anaesthesia of the feet and legs; and a severe bed-sore of the sacral region had developed. At the post-mortem examination a growth was found in the spinal canal at the level of the fifth to seventh thoracic vertebrae, loosely connected with the bone and the spinal dura mater, and compressing the spinal cord. From Eichhorst's description of the micro-

scopical appearances it seems fairly certain that the growth in the spinal canal was of the nature of lymphogranulomatosis maligna, and had developed from lymphatic elements in the peridural (epidural) fatty tissue. Eichhorst himself was not convinced that the case was one of leukaemia. The presence of a considerable polymorphonuclear leucocytosis is quite in accordance with the diagnosis of lymphogranulomatosis maligna, though leucopenia is found in many advanced cases, as it was to an extreme degree in my case (Case I). O. Naegeli and others have drawn attention to the frequent occurrence of considerable polymorphonuclear leucocytosis in lymphogranulomatosis maligna, which Naegeli remarks is not surprising, considering that the disease, according to modern views, is due to a microbic infective agent.

Case III. O. Naegeli (1). Reference is made to a case of lymphogranulomatosis maligna described by Erich Mayer, in which symptoms due to compression of the spinal cord were diminished under treatment by arsacetin. I have been unable to see Erich Mayer's (3) original description.

Case IV. C. W. Suckling (4), 'Case of Lymphadenosis (Hodgkin's Disease), with Multiple Growths from Dura Mater'. This may have been a true case of lymphogranulomatosis maligna.

Case V. K. von Müllern and B. Grossmann (5). Case No. 1. A man, aged 28 years. The growths histologically resembled lymphogranulomatosis maligna, but there was much actual tuberculosis also. Some of the vertebrae were infiltrated with growth, which likewise involved the dura mater, and actually compressed the spinal cord. Microscopically this growth in the vertebrae consisted partly of actual tuberculous material, but also of tissue resembling that of lymphogranulomatosis maligna. This case was probably really one of lymphogranulomatosis maligna, but tuberculosis was certainly also present. The vertebral disease which caused the compression of the spinal cord was at least in part of tuberculous nature. It would be, as Naegeli somewhere points out, not surprising that lymphogranulomatosis maligna should occasionally affect young children or young adults when there are quiescent tuberculous lesions already present in some of their lymphatic glands; perhaps quiescent glandular tuberculosis may be thus activated.

S. Rosentsein (6) described the case of a boy, aged 7 years, with 'pseudo-leukaemia', who became paralysed first in the right and then in the left leg. The post-mortem examination showed disease of the dorso-lumbar region of the spinal cord, but nothing abnormal was found outside the spinal cord in the vertebral canal or in the vertebrae. It seems to me most probable in this case that the spinal cord lesion was due to lymphocytic infiltration, and that the case was not one of lymphogranulomatosis maligna, but of so-called 'aleukaemic lymphadenosis'—allied to leukaemia, but without leukaemic changes in the blood—one of the conditions formerly, and still by some physicians, spoken of under the general clinical heading 'pseudoleukaemia'.

Conclusions.

1. In advanced cases of undoubted lymphogranulomatosis maligna paraplegia or cauda equina symptoms sometimes arise.
2. In Case I and Case II this complication was found to be due to lymphogranulomatous growth within the vertebral canal causing compression.
3. It is highly probable in Case I that the lymphogranulomatous growth

found between the spinal dura mater and the bony wall of the vertebral canal was exactly analogous to the lymphogranulomatous periosteal growth found in the same case outside the bodies (centra) of certain vertebrae. I suppose that the loose connective and fatty tissue within the vertebral canal, between the spinal dura mater and the bone, may be taken as developmentally corresponding to the periosteum outside the vertebrae. Anyhow, both the periosteum on the outside of the vertebrae and the loose connective and fatty tissue (epidural) between the dura mater and bone contain lymphatic elements, in which it is not astonishing that lymphogranulomatous growth occasionally develops in cases of lymphogranulomatosis maligna.

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ADDENDUM (MAY, 1923).

Since writing this paper I have come across a description, by W. B. Warrington, of 'A Case of Lymphadenoma terminating in Paraplegia', *Liverpool Medico-Chirurgical Journal*, 1911, xxxi. 52. The patient was a man, aged 46 years, who was admitted to hospital, in April 1909, with a mass of lymphatic glands on the right side of his neck, of about three years' duration. There was a history of primary syphilis nine years previously, but microscopical examination of an excised cervical lymph-gland showed fibrosis and large mononuclear and a few multinuclear endothelioid cells, characteristic of Hodgkin's disease. He later on developed paraplegia, and died in March 1910. At the necropsy white nodules in the spleen and liver confirmed the diagnosis of Hodgkin's disease. The paraplegia was due to a mass of growth that had eroded the bodies of the eighth to twelfth dorsal vertebrae and had grown downwards along the dura mater, compressing the spinal cord.

Dr. J. R. Charles has kindly written to me of a man, aged about 40 years, suffering from lymphadenoma (Hodgkin's disease). He was first seen in August 1911, but the glandular enlargement had been present for several years. The Wassermann reaction was negative. He developed spastic paresis of the lower limbs in the summer of 1912, but, under Röntgen-ray treatment (of the spine) and arsenic, he gradually regained the full use of his legs. The Hodgkin's disease ran an intermittent course, and he died in May 1916, but had no return of the paraplegia. There was no necropsy.

In the discussion on my case at the annual meeting of the Association of Physicians, in May 1923, Sir W. Hale-White mentioned a case of Hodgkin's disease with upper limb involvement, due to compression of the roots of the brachial plexus by growth within the vertebral canal. Dr. Farquhar Buzzard gave some clinical details of two cases with lower limb involvement.

ERYTHROEDEMA POLYNEURITIS (THE SO-CALLED 'PINK DISEASE')

BY DONALD PATERSON AND J. GODWIN GREENFIELD

With Plate 1

IN March 1922, in collaboration with Dr. Hugh Thursfield, one of us (D. P.) published the report of a case which we called dermato-polyneuritis. This case has since come to post-mortem examination, and we have observed four other similar cases, one of which ended fatally. It has seemed worth while, therefore, to give a full description of these cases, especially as (1) the condition appears to be insufficiently recognized in this country, and (2) in that our post-mortem material gave us fresh evidence as to the essential nature of the malady. Although the literature of the disease contains reports of autopsies, except for one short and unsatisfactory description by Byfield, the microscopic examination of the nervous system appears to have been completely neglected.

Clinical Picture with Mode of Onset.

The age of onset would appear to be between 4 months and 3½ years, but most commonly between 9 months and 2 years. There is the history of an indefinite febrile illness, with coryza and slight bronchitis. In the infants it may be accompanied by vomiting and diarrhoea. This illness is termed a 'cold' or 'influenza'. It may be so indefinite that in a certain number of cases it has not been noticed at all, and the onset of the later symptoms are recorded as the onset of the disease. Following the initial fever, however, there is usually a quiescent period during which the child seems to be recovering, and this lasts as a rule from two to four weeks. In some cases, however, the onset of the secondary symptoms follows almost immediately on the 'cold'.

Mental upset. The child becomes extremely miserable and irritable. Nothing will comfort him, and he refuses to smile or appear pleased at anything. Great stress should be laid on this point, as he presents a picture of utter misery which becomes pathetic in the extreme. There is no hint, however, that the mentality of the child has become affected, as although slow in all his movements he takes notice of what is occurring around him, and recognizes his parents.

Insomnia is marked and he cannot be got to sleep, and during this stage of the disease hypnotics have little or no effect. His parents become worn out with this continual wakefulness, and it is frequently the insomnia for which they seek advice.

Anorexia is constant and extreme. It is difficult to overcome, and, since the wasting is marked, it requires the most strenuous treatment.

The rash, on which so much of the diagnosis depends, appears at the same time as the other symptoms. It commences in some cases as a diffuse erythema all over the trunk, but most marked on the extremities, and commonly it affects the extremities only; the hands, feet, cheeks, nose, and forehead being involved (Pl. I). These become red and swollen, appearing oedematous, but there is no pitting on pressure. This appearance of the hands, feet, and face has been described as a raw beefsteak appearance, or 'as if dipped in boiling water'.

The condition of the hands and feet seems to wax and wane, now being present to a marked degree, now tending to fade.

A fine desquamation occurs on the palms and soles, commencing with small papules about the size of a pin's head, the desquamation extending to the tips of the fingers and toes. Occasionally the desquamation recurs along with the recurrence of the rash.

Perspiration of the whole of the body is marked, and the child, if even moderately warmly clad, is continually damp. If the hands and feet be wrapped up in gloves or socks to prevent scratching, the continual perspiration gives them a sodden appearance.

The extremities appear to be extremely irritable—the child continually scratching and tearing at them, or rubbing them against any convenient object. If the face irritates, he rubs it into the pillow in a burrowing manner, and the tip of the nose becomes bright red.

The attitude in bed is often most characteristic. The child, who from the first seems to show dislike of the light, if not actual photophobia, keeps the face turned to the pillow. The body is in a crouching attitude, the back being curved and the knees drawn up. The face is rubbed from side to side in the pillow. If later the child should sit up in bed, he keeps up continual movements with the upper extremities and upper part of the body as if he were very uncomfortable and irritating all over.

There is great hypotonia of the muscles. This is shown by the lower jaw hanging down so that the mouth is open, and this has been aptly described as giving the appearance of 'a young gosling'. There is no actual paralysis, but the muscles everywhere are toneless, and the limbs may be placed in almost any position. The hypotonia and weakness of the neck muscles may be so great that the child is unable to hold up the head. Because of this hypotonia the abdominal contents can be palpated with the greatest facility.

Ulceration of the tongue or cheeks is common, but is rarely extensive. The teeth and gums appear healthy. In several cases, however, reported by other observers, the teeth have dropped out without obvious disease of the gums.

The hair drops out or is easily pulled out in most cases, leaving large bald areas.

The nails in our cases were not affected, but some observers state that they become loose, or drop off.

The nervous system, however, shows well-marked signs in any advanced case. The reflexes are diminished or absent in the majority; probably the knee-jerks are absent in all cases at some time during the disease.

Sensation to the pain of pin-pricks is lost or greatly diminished over the extremities. Some writers state that in children old enough to answer questions great pain was complained of in the feet and hands, and the child would plead to have the bed-clothes raised from them. There is no actual motor-paralysis—the child being able to make all movements, but feebly, because of the lack of tone in the muscles.

A slight squint was present in one of the cases.

The digestive system shows nothing characteristic apart from the anorexia. Nothing is found in the heart or vessels to account for the redness or swelling of the extremities.

The respiratory system shows a chronic nasal discharge, with mild attacks of bronchitis. A bacteriological examination of the nasal discharge showed the ordinary nasal flora. The Klebs-Loeffler bacillus was never found in our cases.

Smell. A mouse-like odour was noted in two of our cases, while it has been remarked on by other observers.

Temperature. All our cases were afebrile. Some cases reported by others, however, have had a moderate fever for several weeks.

The examination of the *cerebro-spinal fluid* showed no abnormality.

Urine. Beyond a faint trace of albumin, which is usually present during the early part of the disease, nothing else abnormal has been noted. Some writers, however, point out that these cases tend to develop pyelitis as a complication, which reacted quickly to treatment.

The *blood* shows a constant leucocytosis from 15,000 to 40,000—the proportion of polymorphonuclear cells remaining normal, or slightly raised.

Ætiology.

As to the sex, there would appear to be slightly more males affected than females. Wood and Cole state that of 88 cases 52 were males and 36 females. Of these same cases the youngest was 4 months and the eldest 3½ years. Fifteen were under 9 months, and 28 were between 9 months and a year, while 29 were between one year and one and a half years, and 16 were over 18 months.

These cases would appear to commence at any season of the year. There is no special relation between poverty and this condition, as in some of the cases the parents were moderately well off. The disease has been reported from North America and Australia, and now from this country, so it would seem to be fairly widespread, and to be present under varying climatic conditions.

As to what relation the *food* eaten has to the aetiology of this condition there has been a great deal of discussion. There seem, however, to be no grounds for considering it a deficiency disease. Some children have been at an age when they were having 'a little of everything', and others were breast-fed, while others were on a moderately well-chosen mixed diet. In the cases studied by us the diet was above suspicion in every case. No evidence of poisoning by metals such as lead or arsenic has been found in any cases. The gastro-intestinal symptoms of these are not present. There is no blue line on the gums or blood change. In two of Byfield's cases the urine was examined for arsenic and found to be absent. Other members of the family do not show this disease as a rule.

That this is not the result of an *infection* with the diphtheria bacillus seems certain. It is true that there is commonly a chronic nasal discharge, but repeated nasal and throat swabs fail to show the presence of diphtheria bacilli, and other members of the diphtheroid group are present in only a small percentage of cases.

In a few cases reported, *influenza* had been present in the child's family just prior to the onset of the disease. Apart from this the relationship of this disease to influenza is based solely on historical evidence.

Attempts have been made to liken this disease to that described as *acrodynia*, which followed on a pandemic of influenza in Europe in 1828-30.

It would appear that this condition has become much commoner since 1917, and the number of references to it in American and Australian literature has of late increased greatly.

The fact, then, of its undoubted increase in incidence since the great influenza epidemic of 1918 would indicate that there may be some connexion between them. On the other hand, if the cases be gone into carefully, there seems very little to indicate that we are dealing with a manifestation of influenza, and from the pathological findings it appears to be a separate and distinct disease.

Morbid Anatomy.

The microscopical changes in the nervous system in the two cases examined were of similar type, but differed in degree. In the first case (Case I) which came to autopsy the nervous symptoms had begun to improve when the child developed an intussusception and died. In the second case examined post mortem (Case III) the patient went steadily downhill and died from generalized tuberculosis. In the latter case, therefore, the changes in the nervous system were seen at their maximum, and proved conclusively that the disease was a polyneuritis affecting particularly the peripheral parts of the nerve-trunks. A detailed description of these changes will be found in Appendix II, but a general description of the condition may be given here.

Our examination showed considerable myelin destruction in some fibres of the peripheral nerves, increasing in degree and extent on passing to the peripheral

parts of the nerves. In the calf muscles (in Case III) the majority of the finer nerve-bundles were completely demyelinated, and bundles containing ten to twelve nerve-fibres showed complete demyelination of all but two or three. In the popliteal space, on the other hand, only a small proportion of the fibres of the main nerve-trunks showed myelin degeneration.

In the central nervous system in both cases there was a diffuse increase of small cells in the grey matter, especially in the lumbo-sacral enlargement of the cord. This was more striking in Case III than in Case I, but was obvious in both. The nerve-roots also showed some cellular increase, but very little meningeal or perivascular exudate was found. In addition, there were in Case III grave changes of the motor nerve-cells of the ventral horns, particularly in those supplying the distal portions of the limbs. These changes consisted in moderate perinuclear chromatolysis, with eccentricity of the nucleus, and the presence of large vacuoles in the cytoplasm of the cells. This appearance, which is almost always present to a greater or less degree in polyneuritis, probably represents the reaction of the cell-body to degeneration of the peripheral part of the axon.

It was difficult to establish the nature of the cells which gave to the nerve-roots and to the grey matter of the cord the appearance of cellular infiltration. The cells in the nerve-roots were of rather larger size, and tended to be more oval than those in the cord, and appeared to be derived from the nucleated sheath of Schwann; while those in the cord suggested a glial origin rather than lymphocytic invasion. Similarly the great increase of cells in the degenerated calf muscles had, in all probability, arisen from multiplication of sarcolemma nuclei, as a similar appearance is commonly found in the degeneration of muscles which follows lesions of their nerve-supply.

We have, therefore, no clear evidence in our cases of microbial invasion either of the central or peripheral nervous system, although from the histological appearances we are inclined to think that the polyneuritis is due to the toxins of some micro-organism, rather than to a disorder of metabolism such as is postulated in beri-beri and pellagra.

We can, however, exclude the latter diseases on several grounds. The clinical facts which have been already adduced show that there was no dietary insufficiency in our patients; they did not respond so rapidly to treatment as do cases of beri-beri; and the appearance and periodicity of the skin-rash were quite different from those in pellagra. Further, the examination of the central nervous system in pellagra usually gives evidence of myelin destruction in the peripheral fibres of the spinal cord (particularly in the dorsal columns), of which there was no evidence in our cases. And in going through the literature on beri-beri we have failed to find any mention of such a considerable cellular increase in the grey matter of the cord as was observed by us. On the other hand, in 'acute infective polyneuritis' Bashford (1) found very similar microscopic changes in the cord to those which were present in Case III. But in his cases the paralysis was not of a peripheral type, but was usually as great in the

muscles of the thorax and back as in those of the limbs; and there were no signs pointing to affection of the sympathetic innervation of the limbs, such as have been constantly present in the disease under consideration. Therefore, while we are inclined to the view that in this disease the peripheral neuritis is of infective origin, we wish to distinguish it altogether from the condition which has been described under the name of 'acute infective polyneuritis'.

The possibility that it is a form of diphtheritic neuritis was suggested by Byfield (4). He found diphtheroid organisms in the nasal secretion in a large number of his cases, but failed to obtain any clinical improvement by the administration of diphtheria antitoxin; nor was the Schick reaction positive in any case. He found, however, that in many cases the disease came on either with or shortly after a severe cold, and that its course was sometimes considerably shortened by eradication of septic foci in the throat and nose, as by tonsillectomy. As we have already said, the examination of our cases for evidence of diphtheritic infection was uniformly negative.

Historical.

Certainly the clinical picture has been frequently seen in this country prior to 1914. In that year, Swift, of Australia (10), however, first gave the name 'erythroedema' to the condition—a name which serves to indicate the colour of the hands, feet, and cheeks. He states, however, that Drs. Still and Garrod recognized this condition but could contribute nothing to its pathology.

In Australia, Jeffreys Wood (15) and Cole collected nearly 100 cases by 1921, and their description is exceedingly complete. In America, however, a classical description of the disease was given by Byfield (4) in 1920 in an admirable paper with coloured illustrations. It is from Byfield that the first suggestion came that this is a peripheral neuritis, and in the one post-mortem which he reported an attempt was made to examine the nervous system.

We cannot help but agree with Byfield that even from a clinical standpoint we are dealing with a peripheral neuritis mainly involving the sensory nerves, and showing a secondary vasomotor disturbance of the extremities, manifesting itself by the red swollen hands and feet. Byfield says 'the falling out of the teeth without distinct involvement of the gums, the falling out of the hair, point clearly to an involvement of the fifth nerve'.

'The paraesthesia of the extremities and of the trunk suggests a sensory nerve involvement, while the coldness of the finger-tips and toe-tips points to a vasomotor disturbance. The muscular weakness and wasting, the diminution of the reflexes, and at times their complete absence, suggest involvement of the lower motor-neuron.'

Byfield also states that 'if it be borne out by further investigation that we have an infectious polyneuritis, it may be well to dispense with the older names', and we propose to show that there is a definite peripheral neuritis present in these cases.

We have, therefore, proposed the term 'erythroedema-polyneuritis', which retains the name originally given by Swift, and describes the most striking clinical and pathological features of the disease.

Diagnosis.

The picture—when advanced—is so characteristic that there is no difficulty whatever in making the diagnosis. It is, however, very difficult indeed, in the early stages before the rash becomes characteristic and the signs of peripheral neuritis appear, even to venture on this diagnosis.

Once, however, the disease is established, the red hands, feet, cheeks, and nose, together with the loss of muscular tone and the tendon reflexes, the loss of sensation, and the peeling of the palms and soles, present a clear-cut picture. The anorexia, insomnia, perspiration, odour, and blood-count all tend to establish the diagnosis more firmly.

The Prognosis

on the whole is good, and, as a rule, complete recovery takes place in from three to nine months. It is probably because of this that so few post-mortem examinations have been made. In some cases, however, the anorexia leads to extreme emaciation, from which the child may die or be carried off by inter-current disease, especially military tuberculosis.

Treatment.

This consists largely in the treatment of symptoms. It is most important to treat the *anorexia*, and very careful nursing is needed. Attempting to feed the child with a variety of foods, often spoon-feeding because of the sore mouth, or sometimes even feeding by stomach-tube, have to be resorted to. In our experience these children have been able to digest a moderately full diet given in this way.

The *insomnia*, which is so very troublesome in most cases, should be treated with chloral, bromide, chloretone, or trional. Here, again, the nursing is all-important, as if the child be bathed and made comfortable he may fall off to sleep, when with less care a disturbed night may follow.

Some observers state that rapid improvement follows on giving a diet rich in vitamins. We have not found this so.

There seems no doubt, however, of the efficacy of small doses of arsenic and strychnine, especially the latter. The cases were kept for considerable periods on tincture of *nux vomica* with great benefit.

The hands and feet were protected with gloves and socks to prevent their being scratched, and the body clad in light clothing only, so that there was a minimum of sweating.

Conclusions.

1. There is a clinical entity occurring in children between the ages of 4½ months and 3 years, and most common in the second year of life, which presents the following characteristics :

- (a) '*Erythroedema*' : coldness, redness, swelling, and irritation of the hands, feet, cheeks, and nose, with desquamation of the palms and soles.
- (b) Perspiration of the whole body, especially of the extremities, associated with a mouse-like odour and falling out of the hair.
- (c) Extreme mental misery and irritability, insomnia, and obstinate anorexia, with consequent loss of weight.
- (d) Muscular hypotonia, loss or diminution of tendon reflexes, and relative or absolute anaesthesia over the extremities.

2. The disease has a widespread geographical and climatic distribution. It does not appear to be the result of any dietetic deficiency, or of poisoning by lead, arsenic, or other chemical substance ; nor of infection by the bacillus of diphtheria. It appears to have occurred more frequently during and after epidemics of influenza, and is usually preceded by an 'influenzal cold'.

3. There is pathological evidence of peripheral neuritis and of chronic inflammatory changes in the spinal cord and nerve-roots, in which the sensory nerve-fibres are affected more than the motor.

4. The mortality is very low. A few patients have died of asthenia due to anorexia or of complications, such as broncho-pneumonia or tuberculosis. Recovery is complete, with no physical or mental sequelae.

5. Treatment consists primarily in overcoming the anorexia by careful feeding and nursing, and the insomnia by hypnotics.

6. There is some clinical and pathological evidence that the disease is due to a micro-organism, but there is no evidence that it is caused by the same organism as influenza.

APPENDIX I.

All the following cases were admitted to the Children's Hospital, Great Ormond Street.

Case I. Kathleen B., aged 1 year. Admitted 6.3.22. (This case was previously reported by Dr. Hugh Thursfield and one of the writers—D. P.)

This child had been breast-fed for eight months, and appeared perfectly normal up to that time. At nine months she was able to crawl about and weighed 20½ lb. The mother and father are alive and well, and appeared quite healthy. The sister, aged 6, is alive and well. Ten days before the onset of the present illness the child's mother had influenza.

The home surroundings are good.

When nine months old, and when on cow's milk and water, with potato and gravy, as her diet, the child became ill. She vomited frequently for three days, was fretful, peevish, and feverish. The doctor diagnosed 'teething'. The

child appeared better in a few days. A month later the child became irritable, lost her appetite, and wasted rapidly. She continued to whine day and night; at the same time a rash appeared on the hands and feet like white pimples. The hands and feet swelled, became dark red, and then peeled, and had an offensive smell. This rash appeared and peeling took place twice afterwards. There had been periodical fits of screaming, especially at night, and one week before admission a squint appeared. Lately the child had pulled her hair out, especially on the right side.

Her hands irritated her, and she continually rubbed them together. She seemed to have difficulty in swallowing. Her diet at this time was milk, cream, raw eggs, and gravy. For a time she could not hold her head up, but this condition passed off. On admission the child was well covered; the muscles, however, were extremely flabby. She seemed lethargic. The cheeks, nose, and forehead were a bright red colour. The hands and feet were bright red, oedematous, and peeling, and had a curious mouse-like smell. The muscles of the arms and legs appeared toneless, so that the limbs could be placed in any position, and the mouth was kept wide open. A slight squint was present, and on the right side of the head a bald area was present. There was also a slight clear nasal discharge.

The glands were not enlarged. There were sixteen teeth. The tonsils were normal. A small ulcer was present on the tip of the tongue. Nothing abnormal was noted about the lungs, heart, or abdomen. The knee-jerks were active. There was, apparently, a partial loss of sensation, and the child appeared insensitive to pin-pricks. A fortnight after admission the knee-jerks were still present, but possibly less active. The urine still contained a faint trace of albumin, as it did on admission. The cultures of this were sterile. The child seemed to like to turn on its face and burrow into the pillow; she would draw her knees up and curve her back. There was intense sweating of the whole body, and the hands and feet were continually damp. The cerebro-spinal fluid was normal. A throat and nasal swab yielded *Micrococcus catarrhalis* only. The stools yielded *B. coli* on culture; the Wassermann reaction was negative. The red cell-count was normal. The white cell-count showed 18,200 cells per c.mm., with 58 per cent. polymorphs.

The temperature was normal throughout the illness.

This child developed intussusception, and on 8.4.22 died.

Post-mortem. A wasted child; length, 2 ft. 8 in. Weight, 15 lb. 4 oz. Trachea, larynx, lungs, nil. Heart pale, right side distended, weight 3 oz. Liver, 8½ oz., pale and fatty. Spleen, ¾ oz. Kidney, 1 oz., pale. Intestine: ileo-caecal intussusception present, which had travelled round to the splenic flexure. Glands—mesenteric—enlarged; bifurcation not enlarged. Thymus and thyroid normal. Suprarenals and bladder normal. Skin of dorsum of foot appeared normal on microscopic examination.

Sections of all the above organs appeared normal on microscopic examination.

Case II. Dennis B., aged 11 months. Admitted 23.5.22. Discharged 22.6.22.

A full-term child, 9½ lb. at birth, breast-fed for seven months, then on Allenbury's No. 1; then No. 2, and, at nine months, No. 3. Orange juice and grape juice were given, and latterly a new-laid egg, with chocolate, bread and butter, raw scraped apple, and a biscuit or two. There were no previous illnesses.

This was the youngest of six children; the others are all alive and well; so also the mother and father.

The home surroundings are excellent.

At seven months the child appeared to be teething; he seemed fretful and became weaker. At nine months old he came out in a rash all over the lower

part of his body, and on his face and chest, but largely confined to his hands and feet. The rash was extremely irritable—the child scratched at himself and pulled his hair out. At the same time ulcers appeared on his tongue.

He seemed in pain, and screamed incessantly, especially at night. On admission the child was well covered. He was very fretful, and resented examination. A fine scarlatiniform rash was present over the trunk and upper part of the abdomen; the feet and hands were swollen, dark red, and cold, and peeling of the palms and soles was present.

There were four upper and four lower incisors. The mouth was clean, no ulcers being present. The heart, lungs, and abdomen appeared normal.

The knee-jerks were lost, and sensation appeared normal.

31.5.22. The knee-jerks returned. The child assumed the typical attitude in bed—burrowing the face in the pillow with a side-to-side rubbing movement. There was marked desquamation of the hands and feet.

On 5.6.22 the child appeared much more miserable. A nasal discharge was present (negative on culture for diphtheria). The feet and hands became more red, and peeling and a fresh desquamation occurred. He could not be got to sleep at night, although given chloretone.

The urine contained a faint trace of albumin, but was normal on culture.

In June 1922 rash all gone; sleeps well at night; apparently quite recovered.

Case III. Norman C., admitted 16.8.22. Died 9.9.22. Aged 18 months.

He was breast-fed for ten months, and then on nursery biscuits, cow's milk, bread and butter, sponge cake, potato and gravy. At six months he weighed 16 lb.

At ten months he had a feverish attack, which was said to be influenza. There was running from his nose and eyes, and a slight vomiting attack occurred. There was no rash, however. After this the child lost weight. A few weeks later his hands and feet were noticed to be red, swollen, and irritable; the appetite was poor, and the stools were loose and offensive, with occasional slime in them. Cod-liver oil was given throughout the illness.

He was an only child, the father and mother being alive and well, and the home conditions moderately good.

On admission he was markedly wasted, and assumed a typical position in bed, burrowing his face in the pillow. The hands and feet were swollen, red, and cold, and the limbs were markedly hypotonic. There was a peculiar smell about the child, and he was continually bathed in perspiration. Desquamation of the palms of the hands and soles of the feet was present.

A slight nasal discharge was also present, which yielded Hoffmann's bacillus on culture. The mouth was clean, no ulcers being present. The urine was quite normal on culture. The cerebro-spinal fluid was normal, the chlorides being 0.7 per cent. His temperature was normal throughout. He could not be got to sleep, and took his food with great difficulty.

The Wassermann reaction was negative. On 9.9.22 he died suddenly in a convulsion.

Post-mortem. Length, 29 inches. Weight, 13 lb. Brain, 28 oz.—engorged. Caseous areas in upper lobe of the right lung. Miliary tubercles throughout lungs. Bifurcation glands enlarged and caseous. Spleen, $1\frac{1}{2}$ oz. Tubercles were seen on the surface. Kidney, $1\frac{1}{2}$ oz., nil. Heart, $1\frac{1}{2}$ oz., nil. Liver, 12 oz. A few tubercles on the surface. Mesenteric glands enlarged and caseous. Two small ulcers in the lower part of the ilium.

Microscopically diagnosis of miliary tuberculosis confirmed.

Case IV. Bernard R., admitted 30.10.22. Discharged 20.11.22. Aged 13 months.

A full-term child, breast-fed for twelve months. In August 1922 was

perfectly well. The diet was then nursery milk—1½ pints a day—potato and gravy, and bread-crumbs.

The youngest of four children, the others being alive and well; the father and mother also.

When one year old this child could walk. For some few weeks the mother noticed the child losing weight; he had no appetite, and was continually crying, as if in pain. He perspired a great deal and slept badly.

On admission he seemed moderately well nourished. The muscles showed marked hypotonia; the hands and feet were swollen, cold, and reddish-blue. The heart, lungs, and abdomen were normal.

The abdominal reflexes were present and the knee-jerks were absent. The extremities appeared quite insensitive to pin-pricks. He burrowed his head in the pillow in the typical attitude.

4.11.22. The child was most wakeful at night. The appetite improved, and the temperature was normal. The nasal swab was negative for diphtheria. The urine was normal. All the glands were slightly shotty.

On 20.11.22 this child was discharged, knee-jerks being present, and showing a marked improvement. He had, however, not fully recovered.

Case V. Rose B., admitted 3.8.22. Discharged 23.10.22. Aged 1 year and 8 months.

This child was 8½ lb. at birth, and breast-fed for a year. She was then fed on eggs and milk, with a variety of soft foods. She walked at one year, and had not had any other illness. She was the third child, the others being alive and well—her mother and father also.

For one month the child refused her food, got thinner, and went off her legs. She slept in the daytime, but remained awake at night, and the whole of her body was continually bathed in perspiration. Her hands and feet were bright red and puffy.

Her bowels were regular, and there was no vomiting. On admission the cheeks and nose, the hands and the feet, were noticed to be bright red, the latter being swollen and peeling. There was desquamation of the palms and soles. The mouth hung open, and the muscles all over the body were toneless. All the teeth were present, and no ulcers could be seen.

Her lungs and abdomen appeared normal. The weight was 19 lb. The temperature was normal, the knee-jerks were sluggish, and the abdominal reflexes absent. Sensation appeared normal.

The child was extremely miserable, crying and refusing to be comforted.

The cerebro-spinal fluid was normal on examination, the Wassermann reaction negative, and the urine normal in every way.

On 23.10.22 the child was discharged, improved, the knee-jerks being more brisk. Her appetite had returned and the insomnia had disappeared.

APPENDIX II.

Pathological Examination of Nervous System of Cases I and III.

Case I. Pieces were taken for examination from the cerebral cortex, optic thalamus, pons, optic nerves, spinal cord, brachial plexus, vagus, cervical sympathetic, median, and musculo-cutaneous nerves.

Sections of the cerebral cortex, thalamus, and pons, stained by haematoxylin with van Gieson's counter-stain, and by toluidin-blue for Nissl granules, showed no abnormality. The upper cervical region of the spinal cord was also healthy. In the lowest cervical segments and in the lumbo-sacral region of the cord there was a slight, diffuse increase of small cellular elements, apparently of neuroglial origin. The ventral horn-cells were normal. The nerve-roots coming from the

lumbo-sacral segments showed a slight increase in number of the cellular elements of the neurolemma sheath. This may have been accounted for to some extent by the large number of non-myelinated and thinly myelinated fibres going to and from the sympathetic system, but it appeared rather too extensive to be entirely explained in this way. These cells were scattered diffusely among the fibres of the dorsal roots, but in the ventral roots they appeared more sparsely and in patches.

The vagus and cervical sympathetic nerves appeared healthy. In the brachial plexus most of the myelin sheaths and axis cylinders were intact, but here also the nuclei of the neurolemma sheath appeared rather more numerous than normal. With the Weigert-Pal stain the majority of the myelin sheaths appeared of normal thickness. In a few of the smaller bundles all the nerve-fibres were heavily myelinated, but in the majority there was a large number of finely myelinated fibres and some non-myelinated fibres. These fibres may have been of sympathetic origin.

The median nerve showed no Marchi degeneration. All the fibres stained well with haematoxylin, but there was a considerable proportion of fine fibres. Here and there some fragmentation of the myelin could be seen, which was probably due to manipulation of the nerve before fixation.

The musculo-cutaneous nerve showed a certain amount of old-standing degeneration with the Marchi method; and the Weigert-Pal stain revealed a large number of fine fibres, which appeared to be of new formation.

No muscle was examined in this case.

Case III. The brain and spinal cord, the internal and external popliteal nerves, a piece of the gastrocnemius muscle, and a lumbar nerve were removed for examination.

The meninges were everywhere healthy over the brain and spinal cord, and no naked-eye evidence of tuberculosis was made out.

On microscopic examination, no pathological changes were found above the *cervical enlargement*. At this level the capillary blood-vessels were congested, and there was a diffuse increase of small cells, apparently neuroglial in nature, in the grey matter, especially in the ventral horns. Of the large motor nerve-cells in the ventral horns, some were unaffected; others were swollen and of more rounded shape than normal; their nuclei were eccentric, and their Nissl granules pale and displaced towards the periphery. They showed, in fact, a moderate degree of chromatolysis of the type usually associated with lesions of the peripheral nerves. The *thoracic region* of the cord appeared less affected than the cervical enlargement. Most of the nerve-cells were of normal shape, but a few showed eccentricity of the nucleus and vacuolation of their cytoplasm. A slight amount of small-celled infiltration of the grey matter was present at this level also. In the *lumbo-sacral enlargement* the changes were much more definite. The diffuse increase of small round cells was greater, although here, too, it was chiefly limited to the grey matter. The vascular congestion was also more intense, and most of the capillaries appeared to be distended with blood. The ventral horn-cells were irregularly affected. Those of the ventro-mesial and lateral groups remained approximately normal, while the large cells of the ventro-lateral group showed an extreme degree of change. In them the cell-bodies were swollen and contained large vacuoles, most frequently near the periphery of the cell, and sometimes just within the cell membrane; the Nissl granules were scarcely evident, the whole cytoplasm of the cells staining diffusely; the nuclei were eccentrically placed.

The *nerve-roots* of the lumbo-sacral enlargement showed a diffuse or patchy increase of small cells. Some of the ventral and all of the dorsal roots showed this change to some degree, and, in general, to a greater degree than was seen in Case I. In the pia-arachnoid membranes at this level there was also an

accumulation of a few small round cells, which, however, never formed more than a single layer.

The *internal and external popliteal nerves* showed considerable evidence of myelin degeneration, which became more evident on passing distally along the nerves. With the Weigert-Pal stain many of the fibres appeared normal—indeed, at the upper end of the piece examined, the majority were intact—but on passing towards the peripheral end, more damaged nerve-fibres made their appearance. In the latter the myelin appeared either beaded or forming a thin spiral line, while in some the myelin sheath was swollen and stained poorly. In some of the branches of the external popliteal nerve no healthy fibres could be seen; but in other branches of this nerve, and in the internal popliteal nerve and its branches, the proportion of intact fibres was much greater.

In the *lumbar nerve* the Weigert-Pal stain revealed similar changes in a small proportion of the fibres.

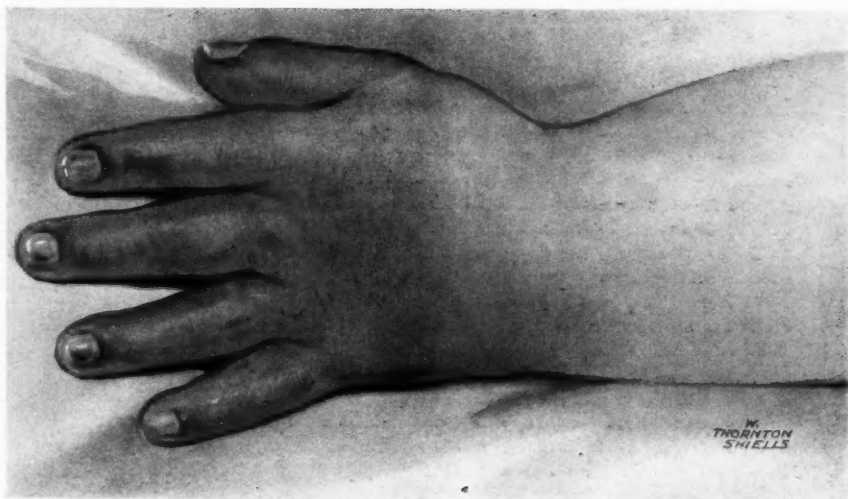
With the Marchi method, both the internal and external popliteal nerves showed droplets of altered myelin scattered along the length of several fibres, but the majority of the myelin degeneration was probably of too long standing to be shown by this method.

The *calf muscle* was stained both by the Weigert-Pal method and by alum-haematoxylin with van Gieson's counter-stain. The former method gave evidence of very considerable degeneration of the small nerve-bundles within the substance of the muscle. In all except the very finest of these bundles some myelin sheaths remained intact, but the majority were beaded or broken up into black-staining droplets of larger or smaller size. Others were swollen and stained poorly, but showed no fragmentation. No single myelinated fibres were seen in the muscle, and the majority of the smaller nerve-branches had lost their myelin completely.

Sections of the muscle stained with alum-haematoxylin with van Gieson's counter-stain showed a general thinning of the muscle-fibres, which had shrunk to two-thirds or less of their normal size. Their outline in cross-sections appeared more rounded than normal, and everywhere there was an excess of sarcolemma nuclei, which in some places gave the appearance of solid masses of nuclear matter between the muscle-fibres. Clusters of small round cells were seen round many of the veins, but most of the cellular increase appeared to be in relation to the connective tissue septa, apparently in the lymphatic channels. The intramuscular nerve-branches showed a slight excess of cell nuclei, which appeared to arise from proliferation of the cells of the neurolemma sheath.

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NOTE THE RASH ON THE HANDS, CHEEKS AND NOSE, WITH THE HALF-OPENED MOUTH, WHICH IS TYPICAL OF THE DISEASE.



THE REACTION TO ADRENALIN IN MAN

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The Object, Scope, and Method of the Experiments.

IN the course of work on adrenalin glycosuria it seemed desirable to investigate some of the other reactions produced by the drug in order to compare them with the changes in concentration of the blood-sugar. About fifty observations have been made on some thirty-five subjects. These include a few patients in whom no abnormality of the ductless glands was present, a number of diabetics and asthmatics, and several cases with thyroid involvement.

Great care was taken to get the subjects into a satisfactory state before the examination was begun. The patients, having fasted for fifteen hours, were put at rest in a quiet room. Preliminary estimations of blood-pressure, pulse-rate, and respiration-rate were made occasionally. A Rosling or a Haldane face-mask was then adjusted, and when the circulatory phenomena had quietened down and the readings had fallen to a constant level, a 10-minute sample of expired air was taken in a Douglas bag for the estimation of the basal metabolic rate.

After this, adrenalin was injected subcutaneously on the outer aspect of the forearm, about two inches below the elbow. The dose usually employed was 0.5-1.0 c.c. of 1:1,000 solution of adrenalin chloride (P. D. & Co.), but smaller amounts have also been given. Following the injection, samples of expired air were collected over 10-minute periods for an hour, and a further sample was taken after an interval of 30 minutes. The carbon dioxide and oxygen percentages in these samples were estimated by the Haldane gas-analysis apparatus. During the whole of the experiment, records of the systolic and diastolic blood-pressures and the pulse- and respiration-rates were taken every two minutes. The data have been examined in various ways, and some of the results are presented below.

Every precaution was taken to avoid sources of fallacy, but difficulties were sometimes met with. The needle puncture seldom caused sufficient pain to disturb the results, though occasionally the pulse-rate momentarily increased 5-20 beats, returning to normal before the next observation (cf. Clough (1)). More rarely there was also a rise of about 5 mm. in the systolic blood-pressure. In two cases frequent samples of venous blood were taken at the same time as

the other examination was being made, and it was noticed that if pain were caused by the needle a secondary rise of metabolic rate, pressure, &c., soon followed, while an increase in the blood-sugar occurred about 20 minutes later. When difficulty was experienced in getting the mask to fit closely there was a temptation to adjust it very tightly. For a time no discomfort would be felt, then, later, pain developed at the points of pressure and caused the patient to worry and fidget. Another important cause of restlessness was the discomfort produced by lying motionless for such a long time. These sensations gave rise to occasional sighs or definite over-ventilation, resulting in an increase in carbon dioxide output, and such reactions could be easily recognized in the graphic records by the presence of a later secondary rise in the metabolic rate. No corresponding increase took place in the circulatory curves in these cases.

When the patient was very emotional, a very irregular series of respiratory quotients would be obtained, but even in such cases the readings of the total metabolism might show a fairly uniform movement. In very unstable cases a sudden loud noise or the appearance of a stranger would cause a slight temporary disturbance which usually showed itself as a rise in pulse-rate, or less often an increase of about 5 mm. in the blood-pressure.

Another difficulty sometimes met with was that the initial levels remained high (apparently from continued excitement). In one case, for example, when the patient's blood-pressure was taken in the general ward it was about 155 mm. Hg, but when she was prepared for examination in the special chamber the systolic pressure would rise to 200, and even a prolonged rest failed to reduce it below 190.

Description of Results.

The administration of adrenalin is followed by a local reaction, and by a general reaction which involves especially the vasomotor system and the general metabolism.

Local reaction. A short time after the hypodermic injection is given there appears a small pale area just proximal to the needle mark. This patch increases in size for an hour or so and may still be visible three or four hours later. It has a rough goose-skin surface, is perfectly blanched, and is usually surrounded by a narrow zone of congestion. In a number of subjects long root-like projections spread from the pale area on to the upper arm. Some of these may follow the superficial veins, while others suggest lymphatic paths. The local pallor is obviously due to occlusion of capillaries and small vessels in the area, and absorption by these is out of the question. Yet in the majority of cases a great proportion of the adrenalin soon leaves the point of inoculation and is probably carried by lymphatic channels to be poured into the general circulation at some point (2). Evidence of rapid absorption is seen in cases of asthma, where relief from dyspnoea occurs a few moments after a minute dose of adrenalin has been given.

Certain phenomena follow absorption. The commonest symptom and the one usually most pronounced is *palpitation*. This begins early and lasts throughout the height of the reaction, passing off as the blood-pressure returns towards normal again. It is present in practically all cases, and may be slight or very severe and distressing. The apex-beat becomes more powerful and can be seen over a larger area, and sometimes the violent cardiac action visibly shakes the whole praecordia. The accompanying subjective sensations may be a vague discomfort, a feeling of distress, or an actual praecordial pain. A beating headache or a throbbing in the head and the great vessels was frequently complained of. Exaggerated pulsations were often seen in the vessels of the neck, and sometimes even in the brachial and radial arteries. Extra-systoles were seldom noted.

In the vast majority of the subjects a fine *tremor* was to be seen affecting the fingers and hands during a considerable part of the reaction. Occasionally there was observed a much more general shaking involving other parts of the body as well as the extremities.

The breathing became deeper and often more irregular in character. The other phenomena were less constant. Circumoral pallor might follow a large dose, but in cases of exophthalmic goitre there occurred a general flushing and an increased moisture of the skin. Profuse sweating took place in one case during a curious spell of hyperpnoea. Increased salivation was sometimes noticed. The pupillary changes were not definite and no lachrymation was encountered. Increased desire for micturition was only found in one patient.

The subjective sensations experienced during the reaction were variously described as a feeling of nervousness, excitement, agitation, apprehension, expectation, or of being 'on edge'. One person likened his condition to that state of tension experienced when one suddenly awakens in the night and listens intently for some expected sound.

Of the other general phenomena examined it is interesting to note that several of them run closely similar courses, rising and falling together and reaching their highest (or lowest) points at practically the same time. This is true of systolic blood-pressure, 'mean B. P.', pulse-pressure, oxygen consumption, carbon dioxide output, respiratory quotient, ventilation-rate, and metabolic rate, which rise, and also of diastolic pressure and the percentage of oxygen in expired air, which fall. Three other curves are quite different from this general type. The percentage of carbon dioxide in the expired air remains practically constant throughout the experiment, the acceleration of the heart-rate occurs late in the reaction, and the apex of the wave of hyperglycaemia in the venous blood appears when most of the other actions are subsiding. So closely do the first group correspond with each other that it would be possible to look upon the fairly continuous systolic pressure-curve as an index of the general reaction.

Types of reaction. Clough (1), in his examination of the circulatory response to adrenalin, classifies his results into four groups according to the severity of the reaction.

	Blood-pressure rise.	Clough's normal cases.	Present series.
(1) Negative or insignificant—up to 15 mm. Hg		30 %	32 %
(2) Moderate	15- 30 "	50 %	30 %
(3) Marked	30- 50 "	12.5 %	34 %
(4) Very marked	50-100 "	7.5 %	4 %

Such an arrangement would only be satisfactory if the blood-pressure had reached a basal level before the adrenalin was given, for it must be obvious that a rise of 15 mm. commencing from 200 would be of much greater significance than a similar increase from 105 to 120. It is true for adrenalin that the effect of the drug is modified by the condition of the individual, equal doses producing varying effects as the initial blood-pressure level is altered (3). To express the increases as percentages of the original pressures would only serve to make matters worse. Another fallacy is that cases of both sexes and of widely different ages may be grouped together, and that the standard dose is employed regardless of size, weight, or body surface.

It seems impossible, however, at the present time to devise a better grouping, but the method should be recognized as unsatisfactory.

Adrenalin acts on the junctional tissue between the sympathetic nerve-ending and the organ innervated. It is rapidly destroyed and is used up quantitatively in producing its effects. The record of these effects should therefore give an indication of the rate at which the substance becomes available for the tissues, and from this curve can also be estimated the rate of absorption of the drug and the amount of it present in the circulation at any moment (2).

The responses to adrenalin in different individuals differ not only in degree but also in rapidity and in form. The reaction might occur with startling rapidity, live a short time, and subside quickly, or the process might be a long-drawn-out affair. The moderate response shows its maximum in the second 10-minute period, and has a fairly gradual rise and fall of pressure, &c. The exaggerated reaction is usually also an early one which reaches its acme in the first few minutes, while slight responses might occur in ordinary time or might be greatly delayed.

The Individual Reactions.

1. *Systolic blood-pressure.* All the subjects examined showed some rise of blood-pressure after administration of adrenalin, even when only 0.1 c.c. was given. In three cases a slight fall of pressure immediately followed the injection, but only lasted about a minute. A secondary fall of pressure below the original level took place in two patients who received doses of under 0.3 c.c. This fall of pressure apparently results from indirect stimulation of the vagus (4), and is commonly seen in experimental animals unless the vagi have been previously resected.

The character of the blood-pressure curve varies greatly from case to case, and even in the same patient under different circumstances. In some the

pressure commences to rise within a few seconds of the injection, while in others four or five minutes may elapse before any effect is noticeable (cf. Clough (1)). The highest point may be reached within six minutes or may be delayed for thirty minutes or more. In nearly half the cases the maximum occurred in the second ten minutes, and of the others the highest point usually appeared in either the third or first periods. Occasionally a greater delay was seen, and in these subjects the late maximum was probably really a secondary rise due to irritation from increasing discomfort. The amount of the increase ranged from 5 mm. (rising from 115 to 120) to 65 mm. Hg (115-180), and in only three was it less than Goetsch's critical 10 points. When the rise was slow and of only a slight degree the maximum level was maintained for a long time, but where a great and sudden increase took place the pressure rapidly fell again. In the majority of cases the reaction had practically passed off at the end of an hour and a half. The rise in the systolic blood-pressure depends upon increased peripheral resistance in a large part of the circulation (principally in the splanchnic area, where in experimental animals all the vessels appear to be occluded), and also on the augmented cardiac output per minute.

2. *Diastolic pressure* is recognized to depend on the state of the peripheral blood-vessels; it represents the dead load of pressure that the heart must overcome at each beat before its action becomes effective in circulating the blood. We have seen that the systolic pressure is always raised by adrenalin, and it is known that the drug contracts *most* vessels. It is surprising then to find that in the great majority of instances a fall in diastolic blood-pressure follows the giving of adrenalin. This must mean that the peripheral vessels in the limbs are relaxed, the stream-bed is increased, the blood-flow is facilitated and augmented. These are the conditions which favour action, as is pointed out by Cannon (5). Von Anrep has noted that the volume of the limbs increases during the rise of blood-pressure following adrenalin (6).

In the cases examined, four types of response by the 'diastolic pressure' have been found: (a) A rise and fall of pressure takes place, the greatest rises coinciding with the maximum of the systolic readings, but being very much less in extent (16 per cent. of cases). (b) A primary short-lived rise of 5-10 points, followed by a fall below the initial level (22 per cent.). (c) The commonest reaction is an immediate fall of pressure with a later recovery. The lowest point is reached when the systolic pressure touches its maximum, so that the dip may suggest a mirror image of the systolic curve, though usually less in degree. (d) In a few subjects the diastolic readings remain practically steady within 5 mm. of the basal level. The greatest reduction in diastolic pressure met with was 35 mm. (from 95 to 60).

In a sense this fall in diastolic pressure might be looked upon as a protective mechanism, a sort of safety-valve to reduce a pressure which threatened to become too high and perhaps damage the vessels. Though the maximum pressure is considerably raised, it is so only during one phase of the cardiac cycle, and this may be largely compensated for by a greater fall during the

opposite phase. A close approximation to the total pressure or the heart's activity during the whole cycle can be got by taking the arithmetical mean of the diastolic and systolic readings. When this is done it is found that in many of the cases, owing to the concomitant fall in the diastolic pressure, the *average pressure* during the cardiac cycle is but little altered throughout the whole reaction. Where a rise occurs the maximum coincides with that of the systolic pressure. The increase is of course most marked where both systolic and diastolic figures increase together.

3. *Pulse-pressure* is believed to represent the effective force of the heart, and great importance is now being attached to this figure. Addis (7) has claimed that by its use he can estimate thyroid activity and so dispense with further estimations of basal metabolic rate in an individual whose basal metabolic rate has once been examined. Several observers (8) have noticed that adrenalin causes an increase in pulse-pressure, and the same has been found in all cases examined in this series. The maximum increase is reached at the same time as the greatest rise in the systolic pressure. In some individuals the difference in pulse-pressure before and during the reaction was very striking: in one the increase amounted to 325 per cent. The range in points was from 20 to 85. These alterations in pulse-pressure are also obvious on palpating or on auscultating the vessel. Sometimes at first in the resting state the sounds over the radial are soft and indistinct, but under adrenalin they become progressively sharper and clearer, and later become softer again. Similar changes are recognizable on palpation.

4. *Pulse-rate.* Adrenalin is believed to have a direct accelerating action on the heart, but this is evidently of less consequence than the augmentor and pressor effects. The heart-rate is ordinarily automatically regulated by a reflex control from the pressure on the walls of the aorta. The rise in intra-arterial pressure produced by adrenalin will stimulate this reflex and, acting through the vagus, will tend to slow the heart. This reflex inhibition is antagonized by the direct action of adrenalin on the sympathetic accelerator nerve-endings in the heart, and the pulse-rate observed is the product of these two forces. The vagal inhibition must also be looked upon as a salutary mechanism preventing undue strain on the system.

The graph of the pulse-rate is quite different from those of the other reactions. It is much less regular in character and more easily influenced than any other by outside conditions. A sudden loud noise or the approach of a stranger may, in a sensitive individual, cause an increase of 10-25 beats per minute over a short period, though the pressure and metabolism remain unaffected. Such rapid changes would appear to arise directly from psychic stimuli.

In the patients investigated, cardiac acceleration always occurred after adrenalin, and in only four was the increase less than 10 points. It begins usually at once, but after increasing a few beats becomes arrested for a time, and then later continues to rise as the other phenomena are subsiding. Often

the increase appears to occur in two definite phases—an early sharp rise which lasts about 10 minutes, to be followed for a time by a slight fall (*vagus*) and later by a greater and more persistent rise. The subsequent return to normal is much slower than in the case of the other disturbances. This would suggest either that the accelerating mechanism is much more sensitive to adrenalin than is the pressor mechanism, and still continues to respond to a much smaller dose when the vessels have ceased to do so, or that the effect of the stimulation on the heart persists longer.

The greatest increase in rate was 85 per cent. (from 65 to 120 beats per minute), and this occurred in a case of hypothyroidism.

5. *Cardiac output and circulation-rate.* No direct evidence of an increased output by the heart has been obtained. The violent cardiac action and the accompanying phenomena would suggest that the volume of blood driven into the circulation in unit time would be considerably increased. Von Anrep, however, thought that in animal experiments the increased blood-pressure in the early stages was accompanied by a dilatation of the heart and a diminished outflow of blood (6). Indirect evidence of the increase in circulation-rate is found in the arterialized state of the venous blood at the height of the post-adrenalin reaction, a state of affairs also found in cases of exophthalmic goitre.

Metabolic Responses.

One of the invariable reactions to the administration of adrenalin is an increase in the general metabolism. This metabolic response appears to be even more sensitive to adrenalin than the circulatory mechanism is, for Sandiford found that in man these changes might occur irrespective of any action on the arterial pressure (9). Nice, Rock, and Courtright report that the metabolism is increased in animals even when the dose of adrenalin is small enough to cause a fall of the blood-pressure (10). The heightened metabolic activity is shown in the increased volume of air breathed and in alterations in the gaseous exchange.

6. *Oxygen consumption.* A marked increase in the quantity of oxygen consumed per minute is regularly found. The average excess over the basal level lies between 20 per cent. and 40 per cent., but much wider extremes are seen. The greatest percentage increase was got in a case of hypothyroidism, the preliminary value of 115 c.c. of oxygen per minute giving place to a maximum of 221 c.c. (92 per cent. increase). The slightest reaction occurred in a diabetic who had been practically fasting for some days. In this case the increase was only 6 per cent. (173 to 183 c.c. per minute). The highest point of the reaction usually occurred in the second or third 10-minute period, corresponding closely in time to the maximum of the circulatory disturbance.

7. The alteration in the *output of carbon dioxide* per minute follows the general reaction, and especially the oxygen consumption. The curve of carbon dioxide excretion is always a little lower than the corresponding oxygen value, but the actual percentile increase is greater, so that the respiratory quotient is

raised during the reaction. Most of the subjects examined show 30 per cent. to 50 per cent. increase in the carbon dioxide output. The extreme figures were 20 per cent. (from 173 to 207 c.c.) and 101 per cent. (from 102 to 205 c.c.).

8. A very different state of affairs is shown by the *percentages* of these gases in the samples of expired air. The concentration of carbon dioxide in the first specimen may be high or low, but this level is maintained with remarkable constancy in the subsequent samples. Sometimes immediately after the injection of adrenalin the carbon dioxide percentage touches a new figure slightly higher or lower than the original one, and this new value is maintained throughout the rest of the reaction—see the last three cases in Table I. This uniformity in percentage in spite of wide alterations in the volume expired is a remarkable confirmation of the importance of this gas in regulating respiration. A selection of CO₂ readings is given in the accompanying table.

TABLE I. *Carbon Dioxide Percentages.*

Before Injection.	After Adrenalin.						
	1	2	3	4	5	6	10
3.30	3.38	3.33	3.39	3.35	3.21	3.22	3.28
3.48	3.55	3.54	3.50	3.36	3.44	3.50	—
3.62	3.75	3.65	3.70	3.70	3.71	—	3.58
2.90	2.95	2.99	2.99	3.02	3.91	2.91	2.72
2.96	3.72	3.78	3.67	3.68	3.68	3.74	—
3.47	2.93	2.80	2.90	2.84	2.92	2.87	2.96
2.70	2.60	2.49	2.55	2.53	2.58	2.57	2.46

9. In the samples of expired air examined after the giving of adrenalin the *percentage* of oxygen falls at first and later recovers although at the same time the *total volume* of the gas consumed is greatly increased. The change begins at once and the minimum value is seen at the same time as the other maxima, so that the curve of oxygen percentage is inverted. The smallest drop was from 4.27 per cent. to 4.16 per cent. in a case of diabetes, the most marked reduction in those suffering from asthma—e. g. from 4.47 per cent. to 3.01 per cent.

TABLE II. *Oxygen Percentages.*

Before Injection.	After Adrenalin.						
	1	2	3	4	5	6	10
4.48	3.99	3.96	4.16	4.18	4.31	4.39	—
4.20	3.65	3.66	4.12	4.39	4.32	—	4.35
3.41	3.01	3.10	3.16	3.24	3.23	3.33	3.62
4.09	3.02	3.16	3.22	3.38	3.54	3.78	—
3.44	2.48	2.62	2.70	2.76	2.80	2.81	2.84
4.18	3.57	3.35	3.84	3.95	2.87	3.80	4.26
3.84	3.52	2.87	2.88	3.11	3.83	3.37	3.99

10. The curious relationship between these gases explains the changes in the *respiratory quotient*. An increase in the respiratory quotient is an invariable feature of the response to adrenalin. The curve expressing the rise and fall of the respiratory quotient is a very regular one, much more uniform than the

graphs of the metabolic rate or of the air expired, since these latter values are more readily influenced by outside disturbances. A metabolic reading must be considerably displaced (e.g. by over-ventilation, &c.) before the corresponding respiratory quotient figure falls out of line. In nearly all cases the maximum respiratory quotient occurs in either the first or second 10-minute period. In about 40 per cent. of the tests the respiratory quotient rise anticipated the metabolic (cf. Tomkins, Sturgis, and Wearn (11)). Sometimes the administration of adrenalin appears to be *at once* followed by a marked alteration in the ratio between oxygen consumption and CO₂ output, so that a very high respiratory quotient is produced in the first 10 minutes. The more rapid the whole general reaction the higher goes the respiratory quotient, and the highest readings are always found in period 1. Of the 15 cases having the respiratory quotient summit in this period no less than six reach unity, and five others exceed 0.95, whereas in all the other groups only three respiratory quotients reached 0.95. These very high readings are difficult to explain. The accompanying phenomena do not suggest that they are due to an abnormal type of ventilation, for the respiratory quotient falls step by step as in other cases, and there is no succeeding period of compensatory low respiratory quotient. It is difficult to see how this regular series of changes in the respiratory quotient extending over an hour and a half could be explained except as a specific effect of adrenalin on the metabolism of the cell. The altered respiratory quotient indicates that a greater proportion of carbohydrate is being utilized by the cell, but this consumption of carbohydrate does not passively follow an increased mobilization of glucose from the liver (12). If Cannon's emergency theory of the action of adrenalin is sound, and there is much to support it, an increased utilization of sugar by the cell is to be expected, for it is much more easily and rapidly made use of than fats. Lusk and Riche (13) have shown that a dose of adrenalin has little or no influence on the nitrogen excretion, so the metabolic and circulatory activities which occur are probably almost entirely performed at the expense of the carbohydrate. An idea of the respiratory quotient changes is got from Table III.

TABLE III. *Respiratory Quotients.*

Before Adrenalin.	After Adrenalin.						
	1	2	3	4	5	6	9
0.774	1.03	0.969	0.839	0.849	0.763	0.780	0.749
0.785	0.866	0.868	0.829	0.847	0.800	0.766	0.832
0.767	0.871	0.792	0.766	0.763	0.738	0.726	—
0.850	0.899	0.987	0.944	0.855	0.805	0.752	—
0.841	0.916	0.965	0.941	0.889	0.896	0.882	—
0.850	0.904	0.907	0.905	0.867	—	0.817	0.815
0.765	0.857	0.876	0.844	0.797	0.778	0.754	0.745
0.776	0.973	0.910	0.841	0.815	0.770	0.783	—
0.790	1.05	0.953	0.951	0.924	0.918	0.870	—
0.725	0.881	0.886	0.776	0.734	0.731	0.727	0.738
0.817	0.931	0.860	0.829	0.772	—	0.799	0.805

11. *Respiration.* In practically all cases the rate of breathing is hardly altered throughout the whole period of investigation. A few subjects show an

increase of two to six respirations per minute. On the other hand, considerable irregularity in the breathing is sometimes found.

12. The most notable effect of adrenalin on respiration is an increase in the depth of each inspiration so that the *ventilation-rate* may be greatly augmented. The volume of air expired may be raised by as much as 60 per cent. over the resting level. Tomkins, Sturgis, and Wearn (11) note that the augmented volume of air breathed per minute may be accompanied by an increased rate or depth of respiration, and that often only one of these factors responds. In the present series of cases any marked increase of rate has seldom been noticed, but in one case of asthma a curious reaction was found. For six minutes after the injection the patient breathed at the same rate as she had previously done, then without warning the rate increased to 30 per minute and the respirations became very shallow. This phase lasted for half an hour and then subsided as quickly as it came on.

The distribution of the maximum values is similar to that of the others already studied, the majority appearing in the second 10 minutes and about equal numbers in periods 1 and 3. Between the volume of air expired and the metabolic rate a very close parallelism exists, so that if the basal metabolic rate has been calculated in an individual and compared with the accompanying ventilation-rate, the subsequent alterations in the volume of air expired would almost accurately express the changes in metabolism. But in two different individuals the ventilation-rate would be of little value in comparing their respective metabolisms.

Few of the subjects were aware of the change in their breathing, but the deeper and easier ventilation after adrenalin was a great pleasure to the asthmatic patients, who felt the change almost at once after the drug was injected. Minute doses of adrenalin suffice to give this relief, and it is known that dilatation of contracted bronchioles may occur independently of any rise in the blood-pressure (14, 15). The action on the bronchial muscle is a specific attribute of adrenalin, but the ventilation changes are essentially secondary to the increased general metabolism.

13. *Metabolic rate.* The details already presented will indicate the changes to be expected in the rate of the general metabolism. Augmentation occurred in all cases; the degree might be great or small and the reaction rapid or slow.

The character of the metabolic responses must depend on the rate of the absorption of the adrenalin, the rate at which it is presented to the tissues, and the sensitiveness of the reacting structures to the stimulus applied. These questions have been more fully discussed elsewhere (2).

14. *Adrenalin hyperglycaemia.* The known influence of adrenalin and of splanchnic stimulation in causing a rapid glycogenolysis and the flooding of the blood with sugar from the liver would lead one to expect to find this reaction in line with the other responses to adrenalin. Cannon's emergency theory of the action of adrenalin would demand that the liberated sugar should be immediately available. It is curious to find, as Hamman and Hirshman have already pointed

out, that the blood-sugar curve is delayed and in no way parallels the rise in systolic pressure (16).

The relationship has been investigated in a number of cases. As painful venipuncture may cause over-ventilation, the sugar examinations were made at another time under similar conditions. In these cases doses of 1.0 c.c. of adrenalin were employed in order to secure a considerable rise in the blood-sugar. As the hyperglycaemia produced is of short duration, samples of venous blood were taken at intervals of 10 minutes. Examined in this fashion the curve of hyperglycaemia appears to differ from all the other curves. The sugar in the blood increases slowly, the maximum occurs late when the other reactions have nearly passed off, and the subsequent decline of the wave is also very gradual.

Tomkins, Sturgis, and Wearn (11) suggested that the general metabolic rise might be due to the hyperglycaemia, and Sandiford (9), supporting this theory, compared the post-adrenalin metabolism curve with the changes described by Lusk (17) as following carbohydrate plethora. But the fact that the two reactions do not coincide in time must negative this idea. Boothby and Sandiford (12) regard the sugar mobilization as an 'interesting compensatory mechanism'. If this be so, why should the compensation overshoot the mark? On the other hand, if the hyperglycaemia is part of a general reaction it is difficult to see why it should be only slowly developing as the main reaction is subsiding.

The amount of sugar in the blood at any moment is the result of the interaction of two factors—the rate at which the sugar is being supplied to the blood and the rate at which it is being removed from the blood. We have here another example of 'consecutive reactions'. What takes place is probably as follows. Some of the adrenalin having reached the blood-stream is carried to the liver. Here, as in other tissues, it acts quickly and directly, increasing the rate of conversion of glycogen into glucose. This ought to raise the percentage of sugar in the circulation, but several factors obscure this effect. The rate of blood-flow is increased during the height of the adrenalin reaction, and if the portal system shares in this acceleration—as seems likely—a very considerably increased output of glucose could be hidden in the blood, provided the blood reaching the liver has no more than the usual concentration of sugar. This would require that the tissues removed sugar from the systemic circulation at a greater rate than normal. This also seems highly probable, for the heightened respiratory quotient shows that the heart and other activated tissues are utilizing a higher ratio of carbohydrate, and in consequence they will make a correspondingly greater demand upon the sugar of the blood. It is suggested that the curve of the rate of discharge of sugar from the liver conforms to the general type (i. e. resembles the blood-pressure graph), but that the greatly increased call of the tissues for carbohydrate causes a rapid removal of sugar from the circulation, so that the increase is masked during the most active period, and only becomes evident in the venous blood when the demand lessens. As the tissue activity subsides the rate of removal of the blood-sugar diminishes, and the percentage of

the circulating sugar increases. The greatest increase of sugar *in the venous blood* appears when the reaction is nearly over, and at about the same time as the pulse-rate reaches its highest level. This prolonged effect, as in the case of the heart acceleration, possibly indicates that the glycogenolytic response is more sensitive than the circulatory reactions. The increased circulation-rate may also aid in the removal of sugar from the blood as well as in the addition of sugar to it.

15. *Glycosuria* results in a considerable proportion of the patients who received 1 c.c. of adrenalin. This waste of sugar is of short duration and never amounts to much. It resembles the transient glycosurias which occur as the result of excitement, anger, or worry in people with a low carbohydrate tolerance—for example, in cases of exophthalmic goitre and in treated diabetics whose margin of safety is narrow.

Type of Case.

Group I. *Cases showing no evidence of endocrine disturbance.* This group, consisting of fourteen individuals, contained a wide variety of responses, so that no single type would be pointed to as normal. The reactions might be slow or rapid, slight and exaggerated. A very active response was usually obtained in those patients clinically recognized as 'nervous' and excitable, but a similar rapid and marked reaction might be given by a subject who showed no such clinical evidence of hypertonus.

Group II. *Cases of hypothyroidism* (six cases). In untreated patients with deficient thyroids the blood-pressure changes are of slight degree and short duration, a rise of 5–15 mm. Hg occurring with the maximum point in about 12–15 minutes. The metabolic increase was something of the same form, but on the whole rather more active than the vascular response. The very slight rise in arterial pressure seemed to remove the necessity for the early vagal inhibition of heart-rate seen in most other experiments, so that an early and moderately extensive rise in pulse-rate might take place (25 to 30 beats). This increase did not last long, and the pulse-rate returned to the resting level in about 20 minutes.

When the cases had been on thyroid treatment for some time, the reactions to a similar dose of adrenalin were considerably enhanced, the blood-pressure and metabolic curves reached a higher level and persisted for a longer time, and although the primary rise in pulse-rate was still prominent a secondary and more extensive one followed as in normal subjects.

Group III. *Hyperthyroid cases* (eleven subjects). The responses to adrenalin in this series are of especial interest because of the use of the reaction as a diagnostic aid (Goetsch's test). Some measure of relationship is evident between the thyroid activity as measured by the basal metabolic rate and the character of the reaction. When the basal metabolic rate is above +40 the response is of an exaggerated type; if it is below +20 the blood-pressure rise may be slow in onset, slight in degree, and rather persistent. In a boy of 20, who had a basal metabolic rate of +54, the systolic pressure rose 44 mm. to its

maximum within three minutes. At the other extreme was a girl who showed very marked exophthalmos but had a basal metabolic rate of only +22. In her case there was a gradual rise of 20 mm. Hg (140-160) to a maximum 25 minutes after the injection. The systolic readings remained practically steady at 160 for forty minutes, and only returned to normal at the end of two hours. In three subjects the diastolic pressure rose after the adrenalin was given, and in four others the values remained practically constant throughout the reaction. This failure to produce the usual fall in diastolic pressure may indicate that the peripheral channels in the arm examined were already greatly dilated, although the diastolic readings actually obtained in the resting state were not lower than usual.

A very prominent feature of this group was the very unstable character of the pulse. Wide differences in rate would suddenly occur from minute to minute, apparently on little or no outward provocation. A transient rise or fall of 20 to 40 beats was quite often seen. The acceleration effect in the most severe cases was very marked (e.g. from 100 to 162), and in these patients an abrupt increase would occur in the first 10-minute period, and thereafter the elevation would increase still further, or at least would be maintained during the whole of the reaction.

The metabolic responses on the whole depended on the activity of the thyroid (basal metabolic rate), but the greatest effects were seen in the middle ranges. When the metabolic rate is just a little above normal the reaction is moderate in degree. Very considerable increases in metabolism take place in those cases where the basal metabolic rate is +30 to +40, but where the resting level is still higher—+50 and over—the amount of metabolic augmentation falls short of expectation. For example, a case with +12 basal metabolic rate rose 28 points (+12 to +40), another with a basal level of 40 above normal increased by 60 points (+40 to +100), while a third patient, starting from +54, only added 38 (+54 to +92). This suggests the application of the logarithmic law (3).

The question of the influence of the thyroid in sensitizing the body to the action of adrenalin has been discussed elsewhere (18).

Group IV. Three patients suffering from *asthma* were studied in the hope that they would offer a sharp contrast to the thyroid cases in whom the sympathetic side of the autonomic system was in a hypertonic state. The responses in some respects are less active than usual, but in each case the systolic pressure and the pulse-rate increase more than the 10 points of Goetsch's criteria. All three subjects remarked on the easier breathing experienced after the adrenalin was given.

Group V. *Cases of diabetes mellitus* (ten cases). The dose of adrenalin employed in this series of patients was 1.0 c.c. of 1:1,000, in order that a marked glycaemia and glycosuria might be produced. Great contrasts were found in the types of reactions obtained, and it was hoped that the results might offer some assistance in distinguishing that group of diabetics in whom a hypertonic sympathetic system plays a large part, from those in whom advanced destruction of the islet tissue was present. This has not yet been found possible.

The pressor reaction ranged from a rise of 10 mm. Hg (over 120) to 75 (over 105), and the maximum elevation occurred from 5 to 35 minutes after the injection. The cardiac acceleration was usually quite marked, the maximum appearing late and the increase being maintained for a long time.

The basal figures for metabolism were in all cases much below normal (-10 per cent. to -27 per cent.) and the initial respiratory quotient was also very low, and in some instances even less than 0.70. The metabolic responses were as variable as the circulatory ones. In one case an increase in only 5 points occurred (from -15 per cent. to -10 per cent.), while the greatest was 33 (from -24 per cent. to $+9$ per cent.).

Several of the patients were examined on more than one occasion, and it was seen that the character of the reaction depended largely on the stage of treatment that had been reached. When the patient was on ordinary food before treatment and again after the preliminary starve, the basal metabolic rate and the respiratory quotient were low, and the metabolic disturbances produced by adrenalin were slight in degree. The vascular reactions might still be considerable at this stage.

As the diet improved the responses increased, suggesting that the degree of the reaction depends in some way upon the store of carbohydrate available.

Summary.

The response to a subcutaneous dose of adrenalin has been studied in a number of subjects.

Local and general phenomena follow the injection. The general reaction includes the production of certain cardio-vascular and metabolic changes—palpitation, blood-pressure rise, and augmented blood-flow, together with increase in pulmonary ventilation, oxygen consumption, and carbon dioxide output, &c. These changes progress nearly synchronously.

The characters of the reaction differ considerably in different individuals. The response may be slight, moderate, or marked in degree, rapid or slow in onset, short-lived, or persistent in duration. The type of reaction depends to a great extent on the rate of absorption of the drug and also on the 'sensitivity' of the patient.

The changes in diastolic blood-pressure, pulse-rate, and blood-sugar concentration do not conform to the general type and are specially discussed.

When the cases are examined from the point of view of the disease present, the changes found are not specially characteristic. Untreated hypothyroid cases show poor reactions, hyperthyroid subjects marked reactions, and in diabetics the character of the response is influenced by the nature of the diet during the preceding days.

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DESCRIPTION OF FIGURES.

Abscissae show minutes before and after the injection of adrenalin, which takes place at the point marked 'M'. The ordinates on the left serve all the data except the percentages of oxygen (J) and of carbon dioxide (K), whose values are indicated on the right of the diagram.

- A = Systolic blood-pressure.
- B = Metabolic rate, as compared with a normal 100 (i. e. 125 = +25 in the more common form).
- C = c.c. of oxygen consumed during 10-minute period.
- D = c.c. of carbon dioxide excreted.
- E = Pulse-rate.
- F = Diastolic blood-pressure (auscultation method).
- G = Respiratory quotient (read ordinates as 0.90, 0.80, &c.).
- H = Litres of expired air.
- J = Percentage of oxygen in sample of expired air.
- K = Percentage of carbon dioxide.
- L = Respiration-rate.

FIG. 1 gives the data obtained from a mild case of exophthalmic goitre (male, aged 26) and illustrates many of the points discussed in the text. The maximum reaction occurs in the second 10-minute period. Notice the preliminary rise in pulse-rate (E) followed by a slower and more persistent rise. The inverted response by the diastolic pressure (F) is marked, and the steady value of the CO_2 is very striking (K).

FIG. 2, from a girl aged 20 who suffered from hyperthyroidism. Note the sudden rise in systolic B. P. after adrenalin. The diastolic readings increase slightly and then fall, while the pulse acceleration occurs rapidly. A short period of vagal slowing is followed by a second maximum and a gradual decline in rate. The volume of air expired in each period (H) is charted to show how closely the figures compare with those of the metabolic rate (B).

FIG. 3 is from the same subject as Fig. 2, a month later, and shows very much the same characters. The metabolic rate rises in each case from +20 to +60; the systolic and diastolic curves are almost the same on each occasion. The maximum increase in pulse-rate is practically identical, but the very unstable character is better seen in Fig. 3. A short period of hyperpnoea is seen during the second 10 minutes.

FIG. 4 is from the same case as Figs. 2 and 3, taken 4 months after Fig. 2. It will be observed that the B. M. R. is now only +2. The blood-pressure reactions are comparatively slight, the metabolic response is still considerable but is somewhat delayed. The increase in pulse-rate occurs much more slowly, but is almost as great as those in Figs. 2 and 3, and since it starts from a lower base line (75 per min.) the percentile increase is greater than on the former occasion.

FIG. 5. A case of exophthalmic goitre (female, aged 25). Shows a moderate reaction, gradual in onset but very persistent. The basal figures were not reached until two hours after the injection.

FIG. 6 is from a case of myxoedema. The systolic blood-pressure only increases 5 millimetres at the height of the reaction. The metabolic response is proportionately greater, but still slight. A short-lived rise in pulse-rate is found.

FIG. 7 shows the reaction of the same subject as Fig. 6 to the same dose of adrenalin after one month of treatment by thyroid extract. The vascular and the metabolic responses are now much larger and occur more quickly. The pulse acceleration is greater, but still shows the same characters as Fig. 6.

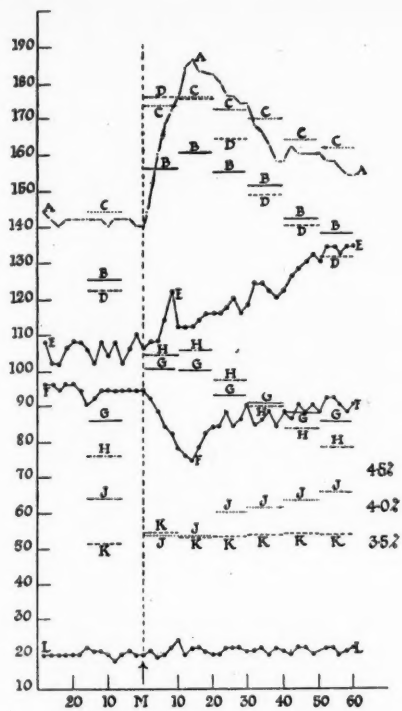


FIG. 1.



FIG. 2.

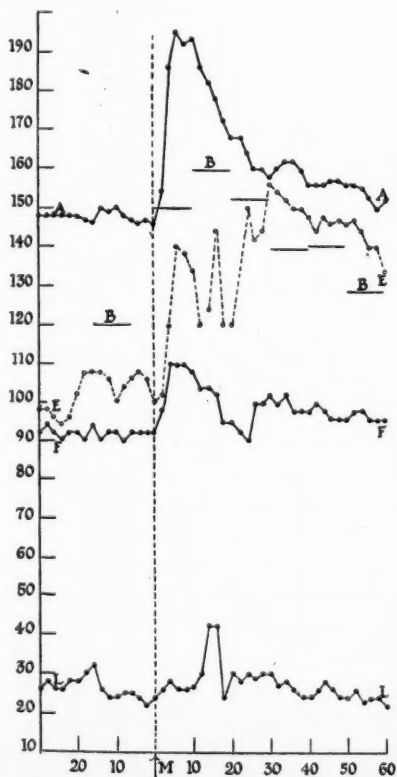


FIG. 3.

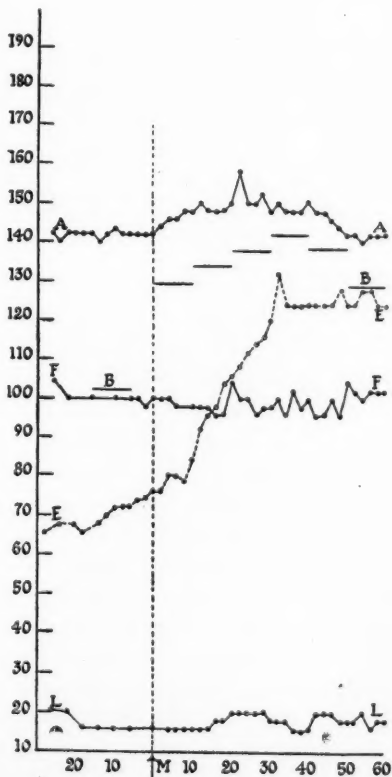


FIG. 4.

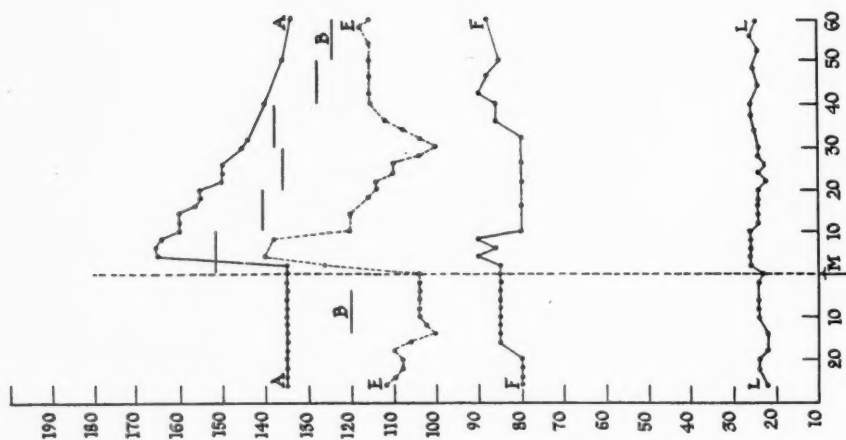


Fig. 5.

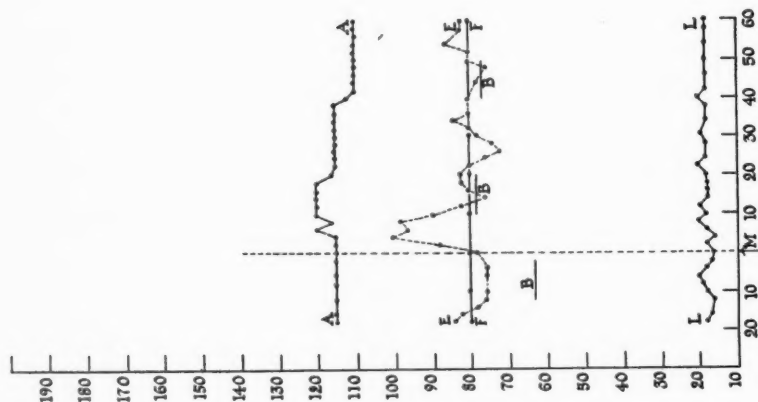


Fig. 6.

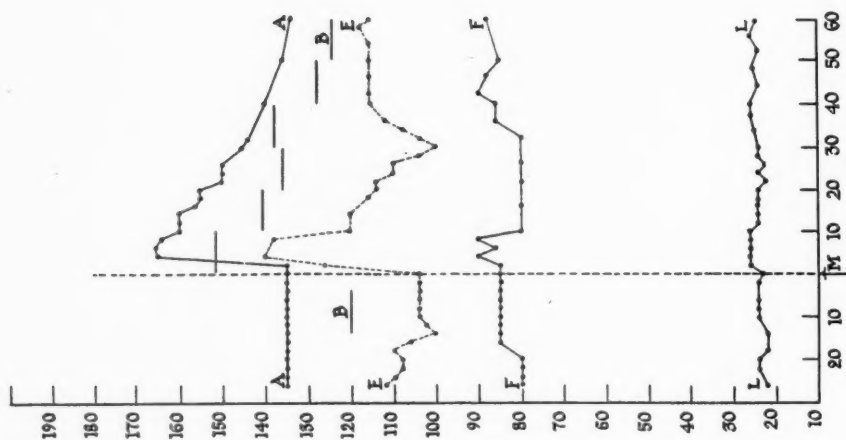


Fig. 7.

THE LAEVULOSE TEST FOR LIVER EFFICIENCY AND AN INVESTIGATION OF THE HEPATIC CONDITION IN PREGNANCY

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Introduction.

METHODS for estimating the functional variations of the organs of the body have always received a large share of attention from investigators. Not only can one thus gain some knowledge of physiological processes, but some light on pathological conditions, and insight into the amount of organic disturbance present, can frequently be obtained. The latter, from a clinical standpoint, is of significance as an aid to diagnosis, and gives additional evidence upon which a prognosis may be based. Investigation of the gastric contents and renal functional tests are now recognized as valuable procedures from this point of view, and on this account they are constantly carried out as a matter of course. Largely, however, owing to the functional complexity of the liver, tests for the investigation of this organ are not so easy of application, and hepatic tests have not yet passed into general use.

In 1901 Strauss (1) formulated a test for liver efficiency, which he based on the differences observed in the urine of normal and pathological cases following the oral administration of 100 gm. of laevulose. In his series of cases with liver affections 90 per cent. showed laevulosuria, whereas only 10 per cent. of his normal control cases exhibited this when tested in a similar manner. In the majority of his positive cases the laevulosuria was observed at the end of the first hour. Churchman (2), who further investigated this test, while admitting it as helpful, regarded it as far from conclusive. He obtained positive results in a number of normal persons, and failed to detect the presence of laevulose in the urine of certain cases of hepatic disease, after using the Strauss test. Wörner and Reiss (3) also carried out experiments on alimentary galactosuria and laevulosuria, and came to the conclusion, in regard to the latter, that its value as a test for liver disease could only be accepted if more than 0.1 gm. was found in the urine, and even then the interpretation of the result needed caution. In as many as eight out of ten normal cases laevulose was

detected by them in the urine following its ingestion. It must of course be obvious that the renal threshold for laevulose is a factor of paramount importance in this connexion, and this point has been specially studied in the following investigation. As it is necessary to eliminate this factor if a test for liver function is to be of value, any method of so doing would necessarily prove a great advance on the above-mentioned methods.

It has been shown by Hopkins (4), Hamman and Hirschman (5), MacLean and de Wesselow (6), and others, that the administration of glucose causes a rise in the blood-sugar values, a definite form of curve being observed. Following a dose of 50 grm. the blood-sugar rises from the fasting level of about 0.1 per cent., and after reaching a value of 0.15 or 0.16 at the end of about an hour rapidly declines. At the end of an hour and a half to two hours, the original level is again reached.

In 1913 Schirokauer (7) carried out a series of experiments on the blood-sugar content, after the oral administration of laevulose, in normal persons, and in those suffering from hepatic disorders. After giving 100 grm. of laevulose he carried out a single blood-sugar estimation one hour later; using the serum and employing Bertrand's method for this purpose he found the rise in the blood-sugar of normal individuals to show a marked difference from that following a dose of glucose. Instead of a value of 0.15 or so being obtained, only the slightest rise in blood-sugar value was noted. In the subjects of liver diseases, however, the rise was marked, values up to 0.19 being observed. At the same time he found laevulose in the urine in the majority of cases, though this did not of necessity show a parallel with the rise in blood-sugar values. Obviously, however significant the differences observed by the above method may be, the disadvantages of this technique are great. Depending upon the processes of metabolism a rise in blood-sugar may occur earlier or later and so pass unobserved.

With the introduction of Bang's micro-chemical method a means was afforded of following closely the alteration of blood-sugar content over a considerable time. The amounts of blood required for repeated observations by this method are so insignificant as to be of no inconvenience or discomfort to the patient. By this means Bergmark (8) showed that fructose, as compared with other sugars, causes only an insignificant rise in the blood-sugar content, observations being carried out by him during a period of two or three hours. This was confirmed by MacLean and de Wesselow (6) in their investigation of sugar tolerance. Based on this observation, the latter observers used laevulose as a test for hepatic efficiency quite independently in the early part of 1920. A further piece of work on this subject was carried out by Isaac (9), who conducted a series of experiments regarding the position of fructose in carbohydrate metabolism. Not only did he confirm the fact that fructose, as compared with glucose, caused no appreciable rise in the blood-sugar content, but he claims to have estimated the relative amounts of laevulose and dextrose in the blood following the oral administration of 100 grm. laevulose. He found in samples

of blood taken from normal persons half an hour, and in other cases one hour, after the administration of this sugar, that dextrose formed by far the greater portion of the total blood-sugar content and that laevulose soon disappeared entirely. In cases exhibiting hepatic disease, on the contrary, not only did the blood-sugar content rise to a much greater extent, but the proportion of laevulose actually present in the blood-sugar was far greater and persisted longer. His analyses were conducted on a protein-free filtrate, estimations being made by a reduction method and by means of the polarimeter. Winter and Smith (10) have been unable to confirm the presence of laevulose as such in the blood. Spence and Brett (11), who carried out blood-sugar examinations after giving laevulose, also observed an abnormal type of curve in cases of hepatic disorder and provided additional evidence of the value of this method as a test for liver function.

This test is dependent upon the fact that laevulose is unable to cause a rise in blood-sugar such as takes place after a dose of glucose. That the liver is concerned in this must be accepted if the test is to be relied on as one for hepatic function. Glucose, we know, is not assimilated and stored as quickly as laevulose. Even in a healthy person its increase in the general circulation is observed by following the blood-sugar curve over a period of one and a half hours. Winter and Smith (10) have claimed to show that the form in which it circulates is that of γ -glucose, this being derived from a common enolic form. The production of γ -glucose is essential before assimilation can take place. Since fructose is probably more easily converted into this enolic form than glucose, it is reasonable to suggest that the conversion and subsequent storage of fructose takes place more rapidly than is the case with glucose. Consequently laevulose does not appear in the circulation to the same extent as glucose immediately following its ingestion. If, however, a pathological condition of the liver exists, then the enzyme or substance causing this conversion may be less active, or so delayed in its action that the fructose, instead of undergoing a rapid conversion into glycogen as is usually the case, circulates in the blood and gives rise to the blood-sugar curve observed in pathological conditions of the liver. It is interesting to note that recent observations made by Bornstein and Holm (12) show a rise of the respiratory quotient immediately after taking laevulose, whereas after glucose this does not occur for forty minutes. A parallel between the height of the blood-sugar curve and the commencement of combustion of the glucose, as indicated by the respiratory quotient, was not observed. They consider that previous to metabolism, glucose was changed into some form of sugar resembling fructose.

Among other tests for hepatic functions Rosenthal's phenoltetrachlorthalein test (13, 14) appears to give satisfactory results, but has not as yet, however, had any extended trial. Another method is described by Hesse and Havermann (15), in which use is made of the administration of sodium lactate followed by observations on the blood-sugar at frequent intervals. Neither of these seem to be placed on so firm a footing or to offer any advantages as tests for hepatic

function over the laevulose test. The value of the haemoclastic crisis in this connexion is also much disputed.

The objects of the following investigation were twofold. Firstly, by an examination of the blood-sugar content after giving a dose of laevulose, followed by a qualitative and quantitative examination of the urine, to come to some conclusion in regard to the renal threshold for this sugar, and to observe the normal variations which it causes in the blood-sugar curve. Secondly, using the above cases as controls, to investigate by the laevulose test the liver function in normal pregnancy. At the same time the urine was tested for the presence of laevulose. It was hoped that observations in these cases of pregnancy would give an insight into normal physiological processes. In the event of liver inefficiency being demonstrable, evidence would then be to hand of liver involvement occurring, to some degree at any rate, in the course of normal pregnancy. This would have a direct bearing on the aetiological factors concerned in the toxic conditions sometimes met with.

Method.

The first series consisted of adult males who were in the medical wards of the hospital. None of them had any clinical signs or symptoms of hepatic disease. They were all in a convalescent stage, and several were getting up and about when the experiments were conducted. They were receiving an ordinary hospital diet, but, prior to the test, which was carried out in the morning, no food was taken for $2\frac{1}{2}$ to 3 hours. This ensured the blood-sugar level being normal at the commencement of each experiment. A specimen of urine was obtained about fifteen minutes before commencing the experiment. A sample of blood was taken from the finger, a dose of laevulose given, and blood examinations made half-hourly up to one and a half hours. The blood-sugar determinations were carried out by MacLean's (16) method. Observations were not continued beyond an hour and a half after taking the sugar, since normally the blood-sugar returns to its fasting level by that period. That this is the case also after giving glucose has been shown by several investigators.

In giving the laevulose we followed the dosage used by Spence and Brett (11). These authors, as well as Churchman (2), consider that the amount given is a factor whether the test be applied to the blood or urine. The amounts given, therefore, were as follows:

To a person weighing 80 kilos	.	.	.	50	gram.	} laevulose.
" " " 60	"	.	.	40	"	
" " " 40	"	.	.	30	"	

It appears that the dosage is of questionable importance, since my results are strictly comparable with other investigators who have used 100 gm. as a routine, irrespective of the patient's weight. Owing to the expense involved, the smaller dose is, however, an advantage, and gives undoubtedly all the

information that is required. One knows that the blood-sugar curve for dextrose is practically identical, whether 50 grm. or 100 grm. of this sugar be used, and it appears also that 30 to 40 grm. of laevulose will give a result similar to that obtained after giving 100 grm. The laevulose was dissolved in about 100 c.c. of cold water. The urine was tested by Fehling's method or with Bertrand's reagent, and the Seliwanoff test employed in the examination for laevulose. Although the Seliwanoff reaction is given by glycuronic acid and by glucose on prolonged heating, a positive result in the urine is unlikely to be obtained when the test is carefully carried out, unless laevulose is actually present. After various trials the method adopted for carrying out this test was that of R. and O. Ardler, as described by Neuberg (17) in his treatise on the urine. Borchardt's modification of the test was also tried, but did not yield satisfactory results. The quantitative methods used were those of Bertrand when sugar was present in any quantity. When traces only were noted, safranin was employed for its estimation. MacLean (18) has shown that this dye is only decolorized by carbohydrates, and is not at all affected by interfering substances present in the urine. Albumin tends to mask the reaction slightly, and the urine should be therefore boiled, and filtered through a starch-free paper. MacLean considers this reagent most useful for determining small quantities of sugar in the urine, the only difficulty being due to the reoxidation which takes place subsequent to heating. During this time the colour quickly returns. This method was adapted in a suitable manner, the above difficulty being overcome by the use of small narrow tubes about 6 mm. in diameter and 12 cm. in length. The procedure was carried out as follows: A 0.1 per cent. glucose solution was made up, a small quantity of toluol being added as a preservative. Into five tubes 2.0 c.c., 1.5 c.c., 1.0 c.c., 0.5 c.c., and 0.25 c.c. respectively were measured. Into a similar set of tubes, corresponding amounts of the urine were placed, and distilled water to make the volume up to 3.0 c.c. is now added. To each tube of both series 1.0 c.c. of a 0.1 per cent. safranin solution, and finally 2.0 c.c. of a 5 per cent. sodium hydroxide solution, were added. The contents of each tube were now shaken up and the tubes simultaneously put into a water-bath of boiling water. For this purpose a small rack, such as is constantly used in the Wassermann reaction, is excellent for holding the tubes. They were allowed to remain $2\frac{1}{2}$ to 3 minutes. The rack was then removed, and the colours of the tubes compared.

By cross-readings a match can usually be effected. Should this not be possible, a fresh set of tubes, containing varying amounts of the glucose solution within a closer range, can be set up. The test is repeated against the amount of urine most nearly approximating to the colour match. Suppose, for example, tube 4 of the sugar solution and tube 2 of the urine show an equal degree of decolorization, we know that tube 4 of a 0.1 per cent. glucose solution contains 0.0005 per cent. glucose. Tube 2 of the urine contains 1.5 c.c. urine; that is, 1.5 c.c. urine contains 0.0005 per cent. glucose. The percentage of sugar actually present in the urine is therefore 0.032 per cent. If the reading be carried out

immediately on the removal of the tubes from the bath, without any undue shaking, and the bottom third of the tubes is used for comparison, the factor of reoxidation in the type of tube described does not enter as a source of error, and results sufficiently accurate for all practical purposes are obtained. In such an alkaline medium a precipitate of phosphates often occurs in the tubes containing the urine. This is, however, not a source of interference and can be disregarded.

The following series of experiments are grouped as considered most satisfactory for comparison, and not according to the dates upon which the experiments were carried out:

	Time.	% Blood-sugar.	Urine.		% Sugar by Safranin.
			Bertrand.	Seliwanoff.	
1. Oct. 26th. W. T. Male, aged 32, ? tuberculosis. Appendicectomy	10.55	0.102	negative	negative	0.1
	11.0	<i>Laevulose 45 grm.</i>			
	11.30	0.117			
	12.0	0.117			
	12.15	—	faint positive	negative	0.20
2. Oct. 30th. W. S. Male, aged 30, convalescent from pneumonia	10.55	0.069	negative	negative	0.025
	11.0	<i>Laevulose 45 grm.</i>			
	11.30	0.074			
	12.0	0.087	negative	indefinite positive	0.025
3. Nov. 9th. W. P. Male, aged 27, ? gastric ulcer	10.35	0.094	negative	negative	0.017
	10.40	<i>Laevulose 40 grm.</i>			
	11.10	0.109			
	11.40	0.117			
	12.10	0.113	negative	negative	0.035
4. Nov. 6th. A. R. Male, aged 28, ? gastric ulcer	11.5	0.094	negative	negative	
	11.10	<i>Laevulose 40 grm.</i>			
	11.40	0.094			
	12.10	0.125	faint positive	positive	
5. Nov. 23rd. H. C. Male, aged 22, ? gastric ulcer	10.45	0.106	negative	negative	0.025
	10.50	<i>Laevulose 45 grm.</i>			
	11.20	0.113			
	11.50	0.12			
	12.20	0.09	positive	positive	0.07
6. Jan. 25th. G. K. Male, aged 33, pericarditis, convalescent	10.50	0.115	negative	negative	
	10.55	<i>Laevulose 50 grm.</i>			
	11.25	lost			
	11.55	0.125			
	12.25	0.104	positive	positive	0.15
7. Nov. 2nd. T. O. Male, aged 26, epigastric pain and fainting attacks	10.55	0.085	faint positive	negative	0.17
	11.0	<i>Laevulose 45 grm.</i>			
	11.35	0.094			
	12.5	0.094	positive	positive	0.30
8. Nov. 20th. E. C. Male, aged 27, influenzal pneumonia, convalescent. <i>Note.</i> Rather nervous patient	11.20	0.136	positive	negative	0.07
	11.25	<i>Laevulose 50 grm.</i>			
	11.55	0.134			
	12.25	0.128			
	12.55	0.128	positive	positive	0.15

	Time.	% Blood-sugar.	Urine.		% Sugar by Safranin.
			Bertrand.	Seliwanoff.	
9. Jan. 11th. H. K. Male, aged 43, gastric ulcer	10.45	0.122	faint reduction	negative	0.075
	10.50	<i>Laevulose 45 gm.</i>			
	11.20	0.117			
	11.50	0.113			
	12.20	0.117	faint reduction	? faint positive	0.075
10. Jan. 29th. J. W. Male, aged 49, gastric ulcer	11.15	0.122	negative	negative	0.05
	11.20	<i>Laevulose 35 gm.</i>			
	11.50	0.117			
	12.20	0.118			
	12.50	0.120	negative	negative	0.034
11. Feb. 1st. E. J. Male, aged 26, normal	10.50	0.109	negative	negative	0.075
	10.55	<i>Laevulose 45 gm.</i>			
	11.25	0.131			
	11.55	0.133			
	12.25	0.115			
12. Feb. 6th. K. H. T. Male, aged 28, normal	12.55	0.113	positive	positive	0.1
	10.45	0.115	negative	negative	0.077
	10.50	<i>Laevulose 40 gm.</i>			
	11.20	0.135			
	11.50	0.128			
13. Jan. 22nd. E. J. Male, aged 26, normal	12.20	0.128			
	12.50	0.117	faint reduction	indefinite positive	0.2
	10.50	0.113	faint reduction	negative	
	10.55	<i>Laevulose 45 gm.</i>			
	11.25	0.137			
14. Jan. 4th. K. H. T. Male, aged 28, normal	11.55	0.131			
	12.25	0.125			
	12.55	0.111	positive	positive	
	10.55	0.115	slight reduction	negative	
	11.0	<i>Laevulose 40 gm.</i>			
15. Nov. 16th. J. L. Male, aged 63, arterio-scle- rosis, B. P. 240/120, mitral incompetence	11.30	0.137			
	12.0	0.123			
	12.30	0.113			
	1.0	0.114	positive	positive	
	10.45	0.117	slight reduction	negative	0.17
	10.50	<i>Laevulose 45 gm.</i>			
	11.20	0.141			
	11.50	0.117			
	12.20	0.117	faint positive	? faint positive	0.1

Analysis.

Group 1. In considering these cases, Nos. 1 to 6 will be taken as Group 1. It will be observed that the blood-sugar never rose above 0.125 per cent. It remained within the limits, practically speaking, of the normal blood-sugar value. Cases 4, 5, 6 definitely showed the presence of laevulose in the urine after the test, in spite of the limit of rise in blood-sugar. By the safranin method an increase in the output of sugar was shown in all but Case 2.

Group 2. Cases 7 to 10 showed to all intents and purposes no alteration in the blood-sugar values. In Cases 8 and 9 a tendency to fall was exhibited. Of these four cases, two definitely showed the presence of laevulose in the urine after the test, and an increase of sugar output as estimated by safranin. The nervousness of the patient probably accounted for the original high blood-sugar value in Case 8.

Group 3. Cases 11 to 15 showed much higher blood-sugar values. Close inspection, however, reveals that the actual rise from the original level is not above those in Group 1. For example, Case 12 showed a rise of less than 20 mg.; whereas Case 3 showed a rise of 23 mg., Case 11 a rise of 22 mg., and Case 4 a rise of 31 mg. Three of this group exhibited a definite positive Seliwanoff reaction. Since the blood-sugar is known to show a tendency to be on the high side in arterio-sclerotic subjects, this probably accounted for the high figure, and an increase of 33 mg. noticed in Case 15.

Before discussing the above, three definitely pathological cases are given by way of comparison.

1. October 18. E. D., female, aged 24. Mucous patches on tongue and inside of the cheek. Liver tender but not enlarged. Wassermann reaction now negative. Jaundice for seven days, most marked. Has had three courses of injections of arsenical compounds and mercury in the past, but not any treatment for eighteen months.

Course I. January-May 1920: 6.30 gr. N. A. B.

Course II. July-November 1920: 6.15 gr. N. A. B.

Course III. March 1921: 2.17 gr. N. A. B.

Time.	% Blood-sugar.	Urine.		
		Fehling.	Seliwanoff.	
3.25	0.104			
3.30	<i>Laevulose 50 grm.</i>			
4.0	0.125			
4.30	0.146			
5.0	0.141			
5.30	0.136			
5.40	—	faint positive	negative	Bile +

2. January 26. D. G., female, aged 35. Tabes and gonococcal arthritis. Has never had arsenical injections, but a course of mercury ten years ago. Jaundice seven days; urethral discharge; slight evening temperature.

Time.	% Blood-sugar.	Urine.		
		Fehling.	Seliwanoff.	
3.5	0.122			
3.10	<i>Laevulose 40 grm.</i>			
3.40	0.191			
4.10	0.178			
4.40	0.162			
5.10	0.125			
5.45	0.114			
6.0	—	positive	positive marked	Bile +

3. December 15. S. K., male, aged 30. Wassermann + + on March 22. Has had a course of arsenical injections and mercury, total 4.8 gr. N. A. B. Last

injection November 7, 1922. Fortnight's jaundice, very marked. Liver not palpable.

Time.	% Blood-sugar.	Urine.		
		Bertrand.	Seliwanoff.	
10.55	0.076	faint reduction	negative	Bile +
11.0	<i>Laevulose 40 gm.</i>			
11.30	0.125			
12.0	0.131			
12.30	0.122	slight reduction	positive	Bile +
1.0	0.114			
1.15	—			

Chart 1 shows three normal blood-sugar curves contrasted with a case of hepatic inefficiency.

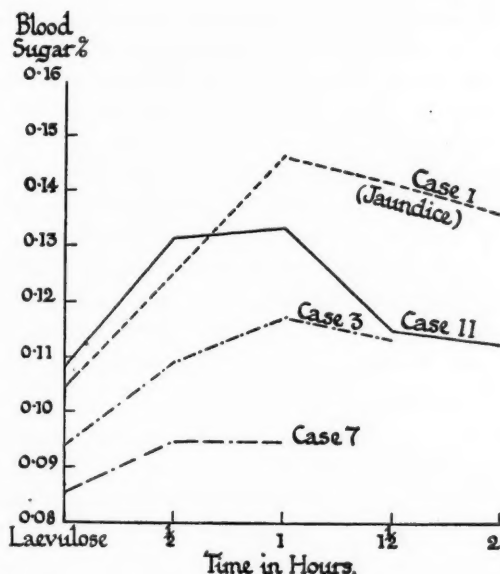


CHART I.

In all these pathological cases, not only did the blood-sugar values rise considerably higher, but the actual increase from the original level is much more marked than in the normal, amounting to 40 mg., 70 mg., and 35 mg. respectively. In addition, it will be noticed that the blood-sugar was still well above the fasting level at the end of $1\frac{1}{2}$ hours. The curve is drawn out and exhibits a typical lag. This, of course, is known to occur also in abnormal conditions following the administration of glucose. It is at once apparent that in the pathological, as contrasted with the normal cases, the height of the curve, the actual rise in blood-sugar values, and type of curve encountered, show a great difference. In persons in whom no hepatic lesion is present the average rise is about 15 mg. The actual height of the curve rarely rises beyond 0.13 per cent, and appears largely dependent upon the blood-sugar level

at which the experiment commences. A fasting blood-sugar value varying from 0.065 to 0.12 per cent. is to be regarded within normal limits. Usually also the blood-sugar curve has returned at the end of $1\frac{1}{2}$ hours to the resting level, as is the case following the oral administration of glucose. The renal threshold is shown to be far lower than is the case for glucose, the majority of normal persons exhibiting a laevulosuria after comparatively small rises, and following upon a very small dose of laevulose. Schirokauer (7) also states that the laevulosuria does not necessarily run parallel with the blood-sugar values.

The renal threshold varies in individuals, but certainly lies between a blood-sugar value of 0.115 and 0.13 per cent. as compared with values of 0.17 and 0.18 per cent., which is the normal threshold for glucose. On this account I regard Strauss's test of little value. It was thought probable that different samples of laevulose, owing to the difficulty of preparation in a pure state, might yield varying values in the blood-sugar. Several experiments were carried out from this point of view, but nothing significant noticed. Individual differences from day to day certainly occur, dependent no doubt upon the general mental and physiological condition of the subject at the time the experiment is carried out. A similar point in regard to glucose has been noted by Graham (19), and nervous influences are known to have an effect on the blood-sugar. For practical purposes a sample of laevulose from any reliable drug house will give satisfactory results in this test, provided that the normal variations are appreciated. We have, however, reason to believe that an absolutely pure laevulose gives, as one would expect, a flatter blood-sugar curve than is noticed after taking a dose of a less pure specimen, in which some glucose is probably present.

With reference to the investigation of the liver in pregnancy by this test, the following experiments were carried out with a view to determining the hepatic conditions towards the end of the term. Women in their seventh month of pregnancy and onwards, who were normal and exhibited no albuminuria or toxic manifestations, were selected from the ante-natal department of the hospital. The blood-sugar was determined, at least $2\frac{1}{2}$ hours having elapsed since their last meal. The laevulose was then given, the dosage depending upon the patient's weight. Samples of blood were examined half-hourly over a period of two hours, and the urine qualitatively examined before and after the test.

In regard to a positive, + denotes a trace of sugar, ++ a very definite, +++ a very marked reaction.

				Urine.		
				Fehling.	Seliwanoff.	
				% Blood-sugar.		
1. Oct. 27th. E. M. Aged 28, primipara, 7½ mos. pregnant		Time.	10.45	0.106	negative	negative
			10.50	<i>Laevulose 50 grm.</i>		
			11.25	0.117		
			11.55	0.122		
			12.25	0.111		
			1.0	—	positive + +	indef. positive

	Time.	% Blood-sugar.	Urine.	
			Fehling.	Seliwanoff.
2. Oct. 20th. M. C. Aged 20, primipara, 8 mos. pregnant	10.45	0-104		
	10.50	<i>Laevulose 50 grm.</i>		
	11.20	0-115		
	11.50	0-109		
	12.20	0-109		
	12.50	0-104	positive + +	positive
3. Oct. 31st. N. H. Aged 38, multipara, 7½ mos. pregnant	10.40	0-100	negative	negative
	10.45	<i>Laevulose 50 grm.</i>		
	11.15	0-117		
	11.45	0-119		
	12.15	0-113		
	12.45	0-07	positive +	positive + +
4. Nov. 10th. E. D. Aged 26, multipara, 8 mos. pregnant	10.40	0-067	negative	negative
	10.45	<i>Laevulose 40 grm.</i>		
	11.15	0-077		
	11.45	0-090		
	12.15	0-067		
	12.45	0-065	positive +	positive + +
5. Nov. 24th. E. W. Aged 26, primipara, 8 mos. pregnant	10.45	0-087	negative	negative
	10.50	<i>Laevulose 40 grm.</i>		
	11.20	0-106		
	11.50	lost		
	12.20	0-100		
	12.50	0-106	positive +	positive + +
6. Nov. 5th. F. K. Aged 27, primipara, 7 mos. pregnant	10.45	0-100	negative	negative
	10.50	<i>Laevulose 40 grm.</i>		
	11.20	0-106		
	11.50	0-115		
	12.20	0-104		
	12.50	0-100	positive +	positive + +
7. Jan. 30. M. T. Aged 20, primipara, 8 mos. pregnant	10.50	0-111	negative	negative
	10.55	<i>Laevulose 40 grm.</i>		
	11.25	0-109		
	11.55	0-106		
	12.25	0-109		
	12.55	0-104	positive + +	positive + +
8. Nov. 8th. C. B. Aged 37, multipara, 7 mos. pregnant	11.0	0-094	negative	negative
	11.5	<i>Laevulose 40 grm.</i>		
	11.35	0-102		
	12.5	0-104		
	12.35	0-094		
	1.5	0-104	positive + +	positive + + +
9. Nov. 17. E. S. Aged 55, primipara, 8 mos. pregnant	10.40	0-094	negative	negative
	10.45	<i>Laevulose 40 grm.</i>		
	11.15	0-113		
	11.45	0-115		
	12.15	0-100		
	12.45	0-097	positive + +	positive + + +
10. Nov. 21st. A. S. Aged 34, multipara, 7 mos. pregnant	11.0	0-104	negative	negative
	11.5	<i>Laevulose 40 grm.</i>		
	11.35	0-111		
	12.5	0-117		
	12.35	0-111		
	1.5	0-112	positive + + +	positive + + +

	Time.	% Blood-sugar.	Urine.	
			Fehling.	Seliwanoff.
11. Jan. 26th. E. P. Aged 25, primipara, 7½ mos. pregnant	10.50	0-097	negative	negative
	10.55	<i>Laevulose 40 grm.</i>		
	11.25	0-113		
	11.55	0-115		
	12.25	0-111	positive ++	positive +++
	12.55	0-092		
12. Feb. 2nd. A. E. Aged 28, multipara, 7 mos. pregnant	10.55	0-104	positive +	negative
	11.0	<i>Laevulose 45 grm.</i>		
	11.30	0-118		
	12.0	0-109		
	12.30	0-102	positive ++	positive +++
	1.0	0-097		
13. Dec. 1st. R. T. Aged 25, primipara, 8 mos. pregnant	10.50	0-100	negative	negative
	10.55	<i>Laevulose 40 grm.</i>		
	11.25	0-125		
	11.45	0-104		
	11.55	0-104	positive +++	positive +++
	12.25	0-077		
14. Dec. 5th. L. B. Aged 23, multipara, 8 mos. pregnant	10.50	0-113	positive +	negative
	10.55	<i>Laevulose 40 grm.</i>		
	11.25	0-156		
	11.55	0-128		
	12.25	0-133	positive +++	positive +++
	12.55	0-133		

Chart II shows three cases of normal pregnancy compared with the blood-sugar curve of a normal control case.

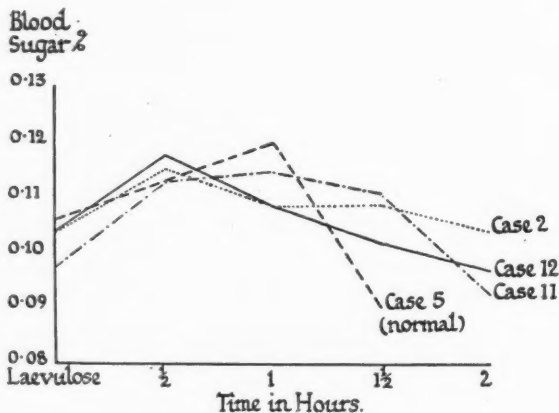


CHART II.

Group 1. Considering as the first group Cases 1 to 7, it will be noticed that the blood-sugar values remained within normal limits, and the actual rise was usually from 15 to 20 mg. All cases showed a definitely positive result with Seliwanoff's test, except Case 1, in which it was doubtful.

Group 2. Cases 8 to 13: the blood-sugar figures are of the same order as in Group 1, but laevulosuria is much more marked. Case 14 stands alone in exhibiting a high blood-sugar value and an actual rise amounting to 44 mg.

From this it appears that the pregnant woman, as compared with the normal, exhibits blood-sugar values which are about equal to those contained in Groups 1 and 2 of the controls, less high than those in Group 3 of that series, and that the actual rises throughout show a variation of the same kind as do the normal; that is, 15 to 20 mg. If anything the rises observed in pregnancy are rather less. It is interesting to note in this connexion, that Bauer (20) found the blood-sugar rises in pregnant women, following upon a dose of glucose, to be less marked, than in normal control cases. Regarding the laevulosuria, it has been shown that the threshold for this sugar is normally very low; that in pregnancy this threshold is practically non-existent appears evident. This is not surprising, since it is known that the renal threshold for all sugars is lowered in this condition. Richenstein (21) made a number of observations in regard to this. In his series of cases he showed that after 100 gm. of glucose, 27.6 per cent. of 65 cases passed a definite amount of sugar in the urine, and an additional 10.7 per cent. showed a trace. After laevulose, he found 87.6 per cent. of 72 cases to present a glycosuria which was quite definite, a further 5.5 per cent. showing a trace of sugar in the urine. Frank (22) regards the lowering of the renal threshold in pregnancy to be the rule. Bauer (20), who examined a large number of women in varying stages of pregnancy, regards the passage of sugar after the injection of 100 gm. as an early sign diagnostic of pregnancy, so usually is it met with. In 120 cases during the first three months of their pregnancy this author was able to demonstrate a glycosuria in 100 per cent. of cases, and 66 per cent. showed it in the later months. In 30 normal controls glycosuria was only once exhibited. Gottschalk (23) carried out a series of experiments on pregnant women. He gave 100 gm. of laevulose to fasting patients, and followed the blood-sugar curve by Bang's method. He also examined the urine hourly. In eight cases he found the blood sugar remained within normal limits, the actual rise being 15 to 20 mg. These, however, did not exhibit a glycosuria, though in two cases bile appeared in the urine. Five cases showed blood-sugar values similar to those cases mentioned above, but a glycosuria was noted. In seven cases he got an increase of blood-sugar values much above normal. A rise of 25 to 35 mg. and a prolonged curve were also noted, and glycosuria occurred after the second hour. My cases in Groups 1 and 2 show an agreement with the above. Only Case 14, however, was observed to give results of the type apparent in his Group 3. The renal threshold encountered in pregnancy, therefore, quite precludes the use of Strauss's test in this condition.

We have only had the opportunity of investigating three cases of toxæmias of pregnancy, these being none too common in hospital wards. Two were women in the pre-eclamptic state in whom labour was induced a few days after admission. One of these subsequently developed eclamptic fits. The

third had suffered fits prior to admission, and labour was induced within forty-eight hours of her arrival at hospital.

January 12. L. E., aged 25, primipara. $8\frac{1}{2}$ months pregnant. Some oedema of legs. Albumin in urine. Numerous hyaline and some epithelial casts. Renal functional tests fair. Blood urea 32 mg. per 100 c.c. Blood-pressure 215/128. 20.1.23 (after induction). Blood-pressure fell to 156/132.

Time.	% Blood Sugar.	Urine.	
		Fehling.	Seliwanoff.
10.40	0.111	negative	negative
10.45	<i>Laevulose 64 gm.</i>		
11.15	0.117	positive ++	positive ++
11.45	0.113		
12.15	0.123		
12.45	0.109		

February 22. E. H., aged 27, primipara. $8\frac{1}{2}$ months pregnant. Slight oedema of legs. No vomiting. Felt well. Urine: albumin + + +. Some hyalogramular casts. Renal functional tests fair. Blood urea 35 mg. per 100 c.c. Blood-pressure 166/120. 26.3.23 (four days after induction). Eclamptic fits developed. 28.2.23. No further fits and patient is doing well. Blood-pressure 156 m.m.

Time.	% Blood Sugar.	Urine.	
		Fehling.	Seliwanoff.
10.45	0.104	positive +	positive +
10.50	<i>Laevulose 40 gm.</i>		
11.20	0.119	negative	positive ++
11.50	0.119		
12.20	0.113		
12.50	0.112		

January 17. M. W., aged 35, primipara. $8\frac{1}{2}$ months pregnant. Oedema of legs since December. Albumin in urine + + +. Numerous hyaline and some epithelial casts. Renal functional tests fair. Blood urea 26 mg. per 100 c.c. Blood-pressure 220/140. 1.1.23. Vomited and had eclamptic fit. 25.1.23 (after induction). Blood-pressure had fallen to 156/130.

Time.	% Blood Sugar.	Urine.	
		Fehling.	Seliwanoff.
10.40	0.090	negative	negative
10.45	<i>Laevulose 50 gm.</i>		
11.15	0.122	positive +	positive ++
11.45	0.136		
12.15	0.128		
12.45	0.128		

The first and second cases showed blood-sugar values within normal range, the actual rise being small. In the third case a rise to just above normal was noted, the actual rise, however, being over 40 mg. and the curve being prolonged. A value of 0.128 per cent. at the end of two hours, as compared with 0.091 per cent., which was the original level, was also observed. The first two cases, in other words, showed no departure from the normal. The third, however, exhibited what is to be considered definite evidence of hepatic involvement. From the above experiments there is no evidence of hepatic inefficiency in

normal pregnancy, but in one case of eclampsia such evidence was forthcoming. Laevulosuria in pregnancy is the rule, following a dose of fructose.

Summary and Conclusions.

1. The laevulose test for hepatic functions is a most useful one, but the normal variations appeared to be rather greater than has hitherto been stated.

2. A blood-sugar value of 0.12 to 0.13 per cent., after a dose of laevulose, is not in itself evidence of a pathological condition. If, however, the height of the curve exceeds 0.135 per cent. and the actual rise in value from the original level exceeds 30 mg. a degree of liver inadequacy is presumed. The prolongation of the curve, a high blood-sugar value persisting at the end of $1\frac{1}{2}$ hours to 2 hours, is strong evidence of such disorder.

3. Dosage according to weight appears to be a questionable factor in the test. 45 grm. of laevulose seem to be satisfactory as a routine dose.

4. A procedure for estimating small quantities of sugar in urine by means of safranin, with the aid of narrow tubes, is described.

5. The renal threshold for laevulose is normally far lower than is the case with glucose, and can be placed at about a blood-sugar value of 0.12 per cent. Since 0.1 per cent. blood sugar is normal, the increase above this which follows the ingestion of laevulose causes the glycosuria; the actual threshold for fructose is, therefore, about 0.02. On this account Strauss's test is of little or no value.

6. There is no evidence that the liver is in any way affected in normal pregnancy. The renal threshold for laevulose in this condition is, however, practically non-existent.

7. Some evidence was obtained pointing to a disturbance of liver functions in certain cases of eclampsia. We have, unfortunately, only had the opportunity of examining two cases definitely exhibiting this condition, and in only one of these was the liver function upset. In the other no changes were apparent.

My best thanks are due to those members of the Hospital Staff who allowed me access to patients under their care, and also to the Medical Research Council for a grant which enabled this investigation to be carried out.

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VISCERAL PAIN IN THE UPPER ALIMENTARY TRACT¹

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With Plates 2 and 3.

General Remarks.

PAIN in the upper part of the abdomen is often attributed to lesions in the stomach and duodenum, but the mechanism of its production is still uncertain. Since the work of Ross, Mackenzie, and Head, at least two types of pain have been thought to exist: the *deep pain*, produced in the viscus and felt deeply in the abdomen, and the *referred pain*, felt superficially on the skin itself, and confined to an area corresponding in innervation to that of the particular viscus.

The literature up to 1910 has been very fully reviewed by Hurst in his Goulstonian Lectures (6), and he has drawn the important conclusion that the viscera only respond with the production of pain if the correct type of stimulus is present. He believes that all visceral pain is due to tension exerted on the musculature of the organ, and that this is the result of distension. The mechanism is somewhat as follows: irritation occurs at a certain spot, due to some lesion; the irritation produces local spasm, or there may be an actual obstruction of some kind. Violent peristaltic waves come down to the spot from above, and as they approach it, the intervening piece of gut becomes completely shut off from the rest of the intestine, the pressure inside it is greatly increased, and this causes increased tension in its walls, and so there is pain. On this theory there must be complete watertight or air-tight closure of a segment of gut. It does not necessarily follow that the walls are in apposition during the descent of the peristaltic wave, because complete closure of a segment might still be produced if there was solid or viscous material in the intervening space to act as a plug.

Hurst also observed that a feeling of painful distension in the stomach was produced when a large amount of gas was suddenly liberated in the organ after

¹ The results in this paper were communicated to the Medical Section of the Royal Society of Medicine (*Lancet*, 1921, ii, 1005). The expenses were defrayed by a grant from the British Medical Association, and the work was carried out during the tenure by one of us (E. P. P.) of a Beit Memorial Research Fellowship.

swallowing sodium bicarbonate and tartaric acid, but he regarded the increase of tension in the whole organ as an infrequent cause of pain in pathological states.

However, it might be said that pain was not due to the increased tension of the visceral walls in Hurst's sense, but that it was due to violent muscular contractions instead. These might be produced reflexly by the pressure of some lesion, by a foreign body, or as the result of some distension of the organ.

In this connexion it must be pointed out that Cannon and Washburn (2) considered that hunger pains were due to contractions of the empty stomach and also of the lower end of the oesophagus. Carlson (3) came to a similar conclusion, and he also observed in the case of a student suffering from gastric ulcer that the pain was associated with contractions of the stomach.

In an investigation of the cause and relief of pain in gastric ulcer one of us (13) has brought forward evidence that a general distension of the stomach plays a more important part in the production of gastric pain than Hurst supposed. Thus, pain was frequently dispelled by the mere passage of a gastric or a gastroduodenal tube, and it could be produced on passing relatively small quantities of air into the stomach.

The method used for measuring the pressure in the stomach was very much the same as that used by Hurst, since a manometer was attached to the tube through which air was passed into the stomach. This was not found at all satisfactory, as any temporary obstruction at the end of the tube in the stomach would give a wrong value for the pressure. Hurst used a wider tube, which might diminish some of the error. It was clear that if any further insight was to be gained into the mechanism of the production of pain, an accurate method of gauging intravisceral pressure would have to be devised, and this is the starting-point of our present experiments.

Methods of Experiment.

Cannon and Washburn (2) and Carlson (3) used an air-balloon for indicating the presence of contractions in the oesophagus and stomach. The movements were communicated by means of a tambour to a kymograph. We have used a small bag containing water. This had the advantage that it could be passed readily beyond the stomach into the duodenum, and beyond the duodeno-jejunal flexure into the jejunum. It has also been passed through a gastrojejunostomy opening into the jejunum. The apparatus is shown diagrammatically in Fig. 1. The end of a Ryle's tube (15) (a modification of Einhorn's duodenal tube) was cut off at A, and the two pieces joined again over a small piece of metal tube. A finger-stall, holding about 20 c.c. of water, was cut out from an indiarubber glove. The Ryle's tube, the rubber connecting tube, the manometer, and the syringe were filled with cold boiled water, with complete exclusion of air, in the following way: The end of the Ryle's tube and the finger-stall were placed in a bowl of the same water, and the finger-stall was bound securely round the tube at A beneath the surface of the water. Owing to

the metal tube inside the Ryle's tube, the finger-stall could be tied on firmly enough to make the joint watertight. The whole system was thus filled with water, and the amount of water in the bag could be accurately regulated by means of the syringe. On squeezing the bag the water passed freely through the holes situated in the neck of the Ryle's tube and rose in the manometer when the tap leading to the syringe was turned off.

If the bag was filled with 8 c.c. of water and held up against the manometer, as in Fig. 1, the level of water in the manometer was found to lie half-way between A and the lead weight at the end of the Ryle's tube. This was the amount of water used in the experiments. If more water was run into the bag, its walls were stretched so that the water in the manometer rose. But with amounts of water between 2 c.c. and 8 c.c. the level of the manometer remained constant.

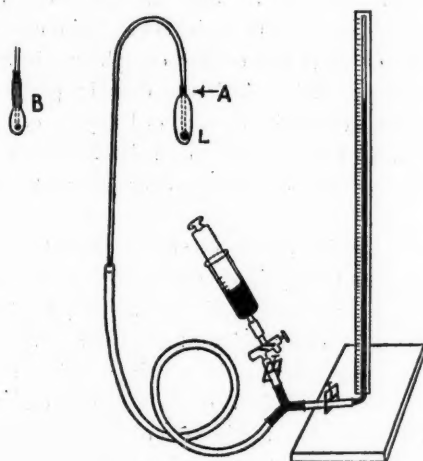


FIG. 1.

Before swallowing the bag, all the water was withdrawn from it. Owing to the metal tube and the lead weight, the bag could be accurately localized and its position determined in any viscus by means of the X-ray screen. In doubtful cases the viscus itself was also outlined by means of a few mouthfuls of bismuth. By such means it was possible to determine whether the bulb was in the stomach, or had passed beyond it into the duodenum or jejunum. After it had been localized and its position marked on the surface of the body, the requisite amount of water was forced into the bag. The manometer was placed on a suitable table close at hand. The zero pressure on the manometer corresponded to the level of the mark on the body surface, and this was determined by a rod with a water-level attached to it. The position of the water in the manometer above or below the zero mark gave at once the actual pressure, positive or negative, in the viscus.

The accuracy of this recording apparatus could be determined outside the body by putting the bulb at the bottom of a tall cylinder beneath a little water. On filling up the cylinder with water, the water in the manometer rose, corresponding all the time with the level of water in the cylinder. As a matter of fact, it was necessary to use a moderately narrow manometer tube so that the bag should not be emptied too much, with a considerable rise of pressure. This meant that there was some capillarity. In the tube actually used the readings were all 1 cm. higher than the true value owing to this factor.

The observations with this apparatus were all carried out in the Medical X-ray Department of the hospital. The room was not a large one, and so it was quite impossible to fit up a self-recording apparatus in it. Instead, observations were made of the manometric excursions at stated short intervals of time, i.e. every 5 or $7\frac{1}{2}$ seconds. One of us called out the time, while the other made the observations. As the time was called out, the subject described his sensations, whether there was no pain, slight pain, or severe pain, and they were noted down. In observations on the oesophagus it was necessary to find out when the patient swallowed. This was done by placing a finger lightly on the larynx. This method was quite capable of bringing out the relation between visceral contractions and the sensation of pain, although later on, when the subject was studied in greater detail, a proper recording apparatus was found to be essential.

At first the actual reading of the manometer was taken when the time was called out, and the points were joined together and formed a curve (see Fig. 4). It was found that large excursions of the manometer might be missed by such means, and in all the later observations two readings were taken representing the size of the excursion at the particular time. They are drawn as vertical lines (see Fig. 2). Small oscillations of 1 or 2 cm. due to respirations were always present. We have taken the bottom of these oscillations as representing the 'mean pressure' in a viscus for the sake of simplicity, though theoretically the mean pressure should be the mean of the respiratory oscillations.

The cause of the larger oscillations requires some consideration. When the bag is situated in a tubular viscus, such as the oesophagus or intestine, we believe that the rise in pressure is due to the walls contracting on to the bag and squeezing it. Sometimes this occurs in the stomach, particularly at the pyloric end. But at the pyloric end, when the stomach is dilated, it is probable that the bag is not itself squeezed, but indicates the actual rise of pressure in the viscus due to contractions in the neighbourhood. In the cardiac end the bag is certainly not squeezed, and we do not find that contractions in the pyloric part cause much alteration in the pressure of the cardiac part, unless the stomach is very small.

The advantages of using a water-bag instead of a bag filled with air have already been pointed out. The disadvantage is that the transmission to the manometer is rather slower than when air is used. The wave is rather drawn out, although it begins at the same time. The apparatus was, however, sufficiently

delicate to show respiratory variations in pressure, and was found to be quite delicate enough for our immediate purpose.

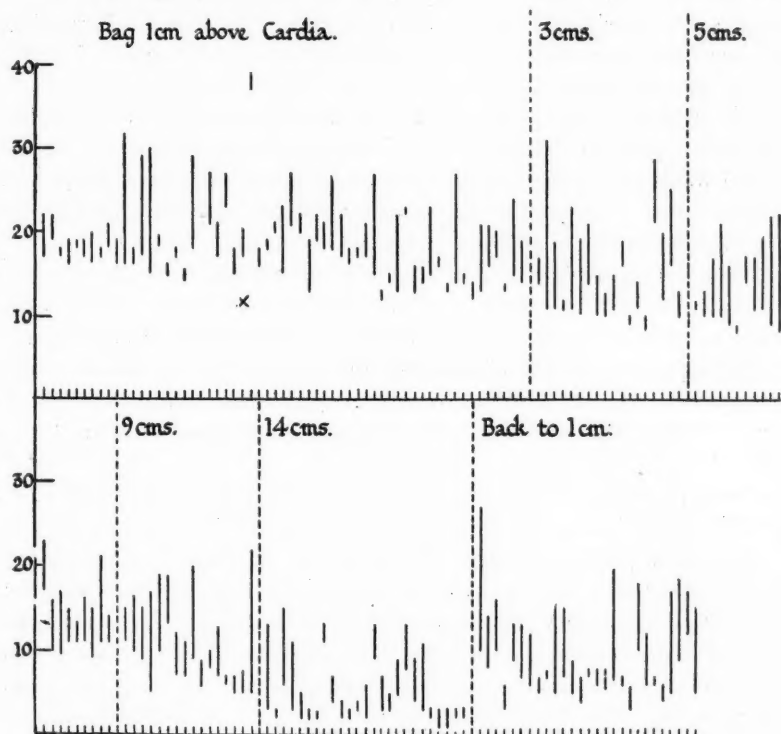


FIG. 2. Ordinate, pressure in cm. of water. Abscissa, time in $7\frac{1}{2}$ " intervals. Subject, W. W. P. x Burning pain noticed at this point. Burning sensations were noticed at intervals; but they were so slight that it was difficult to time them accurately. In the first and last parts of the records, when the bag was situated 1 cm. above the cardia, it was also 1.5 cm. below the right diaphragm.

The Oesophagus.

With the apparatus just described we have been able to observe peristalsis in the oesophagus, and in a general way to confirm Kronecker and Meltzer's results (7). After swallowing, a wave of contraction descends the oesophagus, preceded by a small wave of relaxation. The latter produces a fall in pressure of $\frac{1}{2}$ or 1 cm. of water, and the former produces a large rise of pressure amounting to 30 or 40 cm. in some cases (see Fig. 6). We have made a few observations on the rate at which the peristaltic wave travels by means of two similar bags placed at different levels in the oesophagus. In the case of Wm. Pw. (Case I), who had gastropotosis, and who also had about a month previously symptoms attributed to oesophageal spasm, the bags were placed $3\frac{3}{4}$ inches apart (9.5 cm.) in the lower part of the oesophagus. The time between the rise

in the two manometers was 3.4, 5.0, 3.4, 5.2, 4.2 seconds with successive observations. The mean of these is 4.2; so that the average rate of progression of the wave was rather slower than 1 inch a second. In the case of James We. (Case III), one bulb was placed at the level of the clavicle, and the second 6 inches lower. The time taken between these points was 6.4 secs. and 8 secs., which agrees with the previous reading.

We have also found that peristaltic waves may pass down the oesophagus quite independently of swallowing, especially if the oesophagus is stimulated in some way or is specially excitable. Sometimes a slight movement of the larynx is found to precede such a wave, a movement much smaller than takes place when swallowing is undertaken voluntarily (see Fig. 4).

When the bag is first introduced into the lower end of the oesophagus of an unaccustomed subject considerable contraction may occur. In the case of E. P. P. the mean pressure was 7 cm., and there were contractions roughly every 15 seconds, producing a rise of pressure to 16-19 cm. The subject experienced no sensation; 10 minutes later the oesophagus quieted down considerably. The mean pressure was 5-6 cm. and the contractions only caused a rise of pressure to 10 or 11 cm.

On another occasion a series of experiments were carried out on E. P. P. to test the variation in mean pressure at different levels of the oesophagus.

For more accurate localization the top of the bag was bound tightly to the rubber tube, as at B in Fig. 1. It was thus made much smaller and did not accurately transmit the variations of pressure from the large peristaltic waves, since the volume of water in the bag was too small in comparison with the diameter of the manometer tube, but it gave an accurate representation of the mean pressure. A series of observations with the bag as low as possible, but not in the stomach, showed that the pressure was 13 cm. of water. This represents the pressure exerted at the bottom of the oesophagus. 2 cm. higher it was 9 cm.; at 4 cm., 7; and it gradually fell until at 12 and 16 cm. above the cardia the pressure was negative. This is to be expected owing to the negative pressure of the thorax.

It must not be imagined that there is such a thing as a constant pressure exerted by the oesophagus. The pressure varies with the state of relaxation of the organ, and variable results may be obtained on different days with the same individual without any subjective sensations. Still greater differences result when the subject complains of pain or discomfort. Reference may also be made here to Cannon and Washburn's results on oesophageal contractions associated with hunger pain.

Fig. 2 consists of parts of tracings obtained from W. W. P. over a fairly long period, about an hour. This subject is inclined to mild attacks of dyspepsia. The experiments were undertaken at about the usual lunch-time. He has before noticed slight hunger pains if he does not have his lunch punctually, and on the day of the experiment he was distinctly hungry. The bag was placed as near the cardia as possible, and was the usual finger-stall bag. The

mean pressure near the cardia was 16 cm. to begin with, but it slowly fell to 13 cm. Large oscillations were noticed throughout. There was a curious sensation of a slight burning character at intervals all through, and a definite burning pain was noticed at X, just before the highest excursion of the manometer was recorded. After raising the bulb by 3 cm., the mean pressure was 11 cm., with the same tendency to fall. At 5 cm. it was about the same. At 9 cm. it was about 6 cm. pressure, and at 14 cm. it was +2 cm. This was the highest point at which the bag could be tolerated without vomiting. There was no place in the oesophagus, on this occasion, where the pressure was negative as with E. P. P., though on other occasions negative pressures in the middle of the oesophagus have often been recorded with W. W. P. The bag was then lowered again, and it will be seen that the lower end of the oesophagus had then relaxed as with E. P. P. The mean pressure was about 4 cm. Large oscillations, which will be shown to be due to peristaltic waves, were present throughout.

The Cardia.

Majendie (10), about a hundred years ago, observed alternate contractions and relaxations at the end of the oesophagus of a rabbit immediately after death. This phenomenon is also known as Basslinger's pulse, and Schiff (16) observed that the wave of contraction involved the lower end of the oesophagus as well as the cardia. However, he thought that the wave moved alternately up and down. We agree with Cannon (1) that this interpretation is wrong; there is no anti-peristaltic wave. We should also like to refer to quite recent papers by Carlson and his co-workers (4) detailing experiments on the oesophagus and cardia of animals. Our interest was particularly aroused by the observations of Kronecker and Meltzer (7); we have confirmed these, and we will now proceed to describe exactly what can be seen at the end of the oesophagus in a rabbit immediately after death.

On opening the stomach and touching the cardia or the oesophagus in its neighbourhood, the lower part of the latter contracts longitudinally and circumferentially and at the same time descends and becomes invaginated into the stomach. The effect of this movement is to cause a simultaneous lengthening and slight narrowing of the rest of the oesophagus in the thorax. The main part of the oesophagus is in fact pulled upon. This movement causes a firm closure of the bottom of the oesophagus. The appearance is reminiscent of the firm closure of the anus that occurs after defaecation; the whole action is in fact very similar to what can be seen immediately after defaecation in the horse. On relaxation of the cardiac sphincter the oesophagus shortens, the invagination disappears, and the cardiac orifice becomes patulous. We have found that this relaxation can be brought about by stimulating the vagus. On cutting up the oesophagus longitudinally, the part of the muscle that takes part in the movement is seen to be only a very little bit thicker than the part above, especially if it is cut up after complete relaxation of the sphincter has occurred, and it is

noteworthy that the part of the oesophagus that takes part in the process extends for some little distance above the diaphragm. This observation suggests that the cardiac sphincter is in reality the bottom part of the oesophagus, in the same way that the ileo-caecal valve is the end of the small intestine.

We have tried to find out whether these observations are applicable to man. On cutting up the oesophagus and cardiac opening longitudinally at post-mortem, the muscle of the lower two or three inches of the oesophagus may often be seen by the naked eye to be thicker than the muscle of the oesophagus immediately above.



FIG. 3. Two diagrams showing position of the bulb during contraction and relaxation of the cardiac sphincter. Subject, W. W. P.

We have obtained evidence that the oesophageal sphincter does descend in man as in the rabbit, and that it does contract during its descent. The water-bag was swallowed, and placed as low in the oesophagus as possible. The lower weight L (see Fig. 1) was seen as in B (Fig. 3). The pressure indicated by the bag in this position (subject, W. W. P.) averaged about 24 cm. of water. The subject swallowed, and about 15 sec. later the weight was seen to descend and actually to project into the air-bubble of the stomach as in A. Simultaneously the pressure rose to from 34 to 40 cm. The weight was then seen to be suddenly kicked, as it were, upwards as in B, while the pressure fell to 24 cm. again. During the descent of the bag, W. W. P. experienced a distinct drag on the tube, but no unpleasant sensations. The rise and fall of pressure took place at about the same rate. Although these observations are compatible with the theory of the cardiac sphincter described above, they do not prove that the oesophagus itself is invaginated into the stomach. The contraction wave might have pushed the weight in front of it and the sphincter might have exerted sufficient pressure on the upper part of the bag to cause the rise in pressure noted. These observations do, however, suggest that the oesophagus descends. We observed exactly the same phenomenon in the case of the patient Dan K. The movement upwards of the weight was probably exaggerated by the fact that when the weight descended, during contraction of the cardia, the rubber tube was put on the stretch, and this made the weight fly back quicker than it otherwise would have done.

Gastro-oesophageal Anti-regurgitation Reflex.

Kronecker and Meltzer (7) described a prolonged contraction of the oesophagus after drinking aerated water. They did not determine whether this was due to stimulation of oesophagus or stomach. Cannon (1) has found in animals that the presence of acid in the stomach increases the tone of the cardia and stops regurgitation movements. We have investigated the question by getting subjects first to drink some water containing sodium bicarbonate enough to produce 500 c.c. CO_2 , and then a little extra water to wash it down with, and

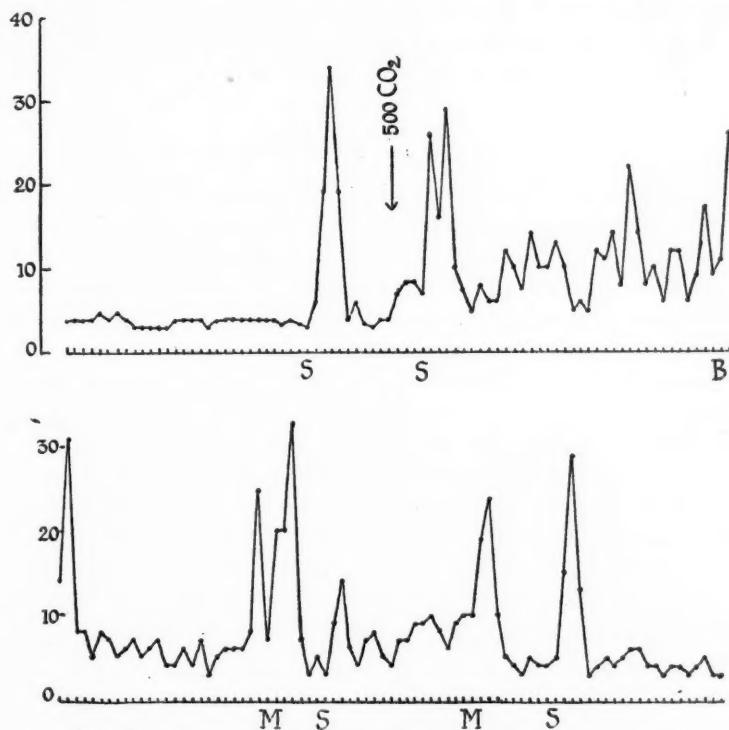


FIG. 4. Pt. M. Ordinate, as before. Abscissa, time in 5" intervals. s = swallow. M = small involuntary movement of larynx. B = borborygmi.

subsequently an equivalent amount of citric acid. The experiment was carried out on E. P. P. with the bulb made smaller by binding the upper part as explained already. The experiment was the last one carried out that day, and the oesophagus was relaxed as shown by the pressure, which was only 4 cm. when the bag was 1 cm. above the cardia. A slight increase in the oscillations was observed half a minute after swallowing the liquid, but the greatest effect was observed $1\frac{1}{2}$ minutes later, when a sensation of bubbling was experienced. After two contractions causing the pressure to rise 13 cm., the pressure was sustained at 16 cm. for nearly half a minute with small oscillations of 1 or 2 cm. about this

level. It then suddenly fell to the original 4 cm. level. There were no unpleasant symptoms.

Some more observations were carried out on a patient, M., who had some dyspeptic symptoms, which were attributed later to a carcinoma caeci, causing some very chronic intestinal obstruction. The complete experiment is shown in Fig. 4. The mean pressure of the oesophagus was 3 cm. The effect of a voluntary swallow is also shown. After giving the sodium bicarbonate and citric acid the oesophageal pressure rose to 8 or 10 cm. and there were numerous contractions. Some of these were due to swallowing, others followed the slight movements of the larynx already described. The effect of the CO_2 gradually passed off and the final state of the oesophagus was much the same as before. A similar result has been obtained by us, on distending the stomach with air.

Abnormalities of the Oesophagus.

Oesophageal pain. Ross (14) described visceral pain of two kinds: (1) Deep pain felt in the affected viscus; (2) pain referred to the skin. Head (5) and Mackenzie (9) believe that referred pain arises from the same segment of the spinal cord as supplies the affected viscus. Mackenzie goes farther and says that all visceral pain is referred. One of his arguments is that gastric pain is often felt in the epigastric angle, which is not situated over the stomach at all, but is much higher up. Hurst (6) has pointed out some of the objections to these views of Mackenzie's.

We have been able to answer the particular argument of Mackenzie mentioned above, by finding out that pain felt in the epigastric angle is really due to events occurring in the lower end of the oesophagus. In fact we have come to the conclusion that pain in this region, so often described as 'heart-burn', is associated with some kind of tonic contraction, and with intermittent contractions and relaxations of the muscle. Further, in a preliminary communication (12) we have indicated that pain may occur during the relaxation, and is then probably due to stretching of nerve-fibres in the wall. This latter hypothesis was suggested by Majendie (11).

We would point out here that the position of the pain usually corresponds in level fairly accurately with the part of the oesophagus affected. Referred pain is indicated by the tenderness felt in the skin when it is stroked, or lightly taken up between the finger and thumb. The true visceral pain is felt deeply and appears to be situated in the organ itself. Our attention was first drawn to the pain associated with the oesophagus by the following case:

Case I. William Pw., a warehouse foreman, aged 36. Appendicectomy was performed nine years before and he had had constipation since then. History of epigastric pain since August 1920. Admitted March 21, 1921. X-ray showed gastroptosis. Fractional test-meal showed absence of free HCl. He was fitted with a Curtiss belt and used at the same time a small conical pad as advised by Leven (8), so as to exert greater pressure on the lower part of the abdomen.

One day he had come to Out-patients, complaining of two pains which he

had not noticed before, one at the top of the sternum and the other over the xiphisternum. A radiogram (see Plate 2), taken in the oblique position, showed clearly a persistent narrowing of the oesophagus at the top of the thorax and also at the bottom.

Observations were carried out with the bag in the position of the upper constriction, and at the cardia. In the former place the mean pressure was -2 cm. (see Fig. 5). However, there are large contractions placed at intervals, and the increase of pain is associated with these.

A very similar tracing with large contractions was obtained with the bag in the lower part of the oesophagus; but the mean pressure was $+12$ to 15 cm. He was paying attention to the upper pain felt at the inner end of the first right intercostal space when the upper part of the oesophagus was being investigated with the bag, and to the lower pain when the lower part was being investigated. The position of the latter pain was described as being either beneath the right costal margin, or between this and the umbilicus behind the right rectus muscle.

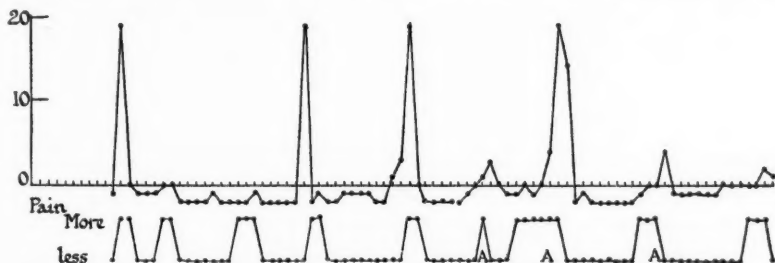


FIG. 5. Case I. Bag in constricted part of upper oesophagus. Time, 5" intervals.

We have subsequently found by using two bags at different levels that the big contractions were due to peristaltic waves passing down the oesophagus. They were obviously associated with the pain, but close inspection of the diagram will show that the pain usually increases just when relaxation is beginning, and occasionally, as seen at A (Fig. 5), the contraction diminishes the pain (12). This will be dealt fully with in a later communication. Since pain in both situations was obviously associated with peristaltic waves, it made little difference to the result whether the subject paid attention to the upper or the lower pain. We obtained a very similar relationship between the pain and the contraction with the bag in the lower part of the oesophagus, whether the patient's attention was directed particularly to variations in the lower pain or to the upper pain. It should be mentioned that, though these peristaltic contractions were similar to those obtained on swallowing, the majority of them were not due to this, but were no doubt 'secondary' peristalsis due to irritation of the oesophagus.

Some more patients were examined in a similar manner, in order to see whether the relationship between pain and oesophageal movements held good in their case also.

Case II. John Cl., a watchman, aged 63. History of pain in epigastrium off and on for five years. Admitted with a severe attack on May 4, 1921. X-ray showed some delay in emptying of the stomach, and fractional test-meal showed delay with 'climbing' free HCl curve. Faeces gave a strongly positive guaiac test but no blood spectrum. Diagnosis, 'parapyloric ulcer'. Patient did very well with rest in bed and dieting and gained 16 lb. in weight.

When the patient was examined on June 10, he had noticed some pain in the mid-line situated about the lower end of the sternum. Fig. 6 gives an extract from what was observed. The pain was continuous, though it apparently

fluctuated a little in intensity occasionally. The mean pressure was about 30 cm. and there were in addition big contractions of the oesophagus taking place. On June 23 the pain had disappeared completely for some days. The pressure was if anything low, beginning at 8 cm. with rather high contractions, due to stimulation by the presence of the bag. It ended off at 3 cm. and the excursions were much smaller. When the patient swallowed at the end, the contraction was as high as any of those which he had had when the pain was being experienced.

Case III. James We., a printer, aged 48. History of indigestion for 18 months. Admitted June 5, 1921. X-ray—small hypertonic stomach which emptied rapidly. Test-meal showed highly acid resting juice and extreme hyperchlorhydria. The stomach emptied rapidly and there was continued secretion. Diagnosis, duodenal ulcer.

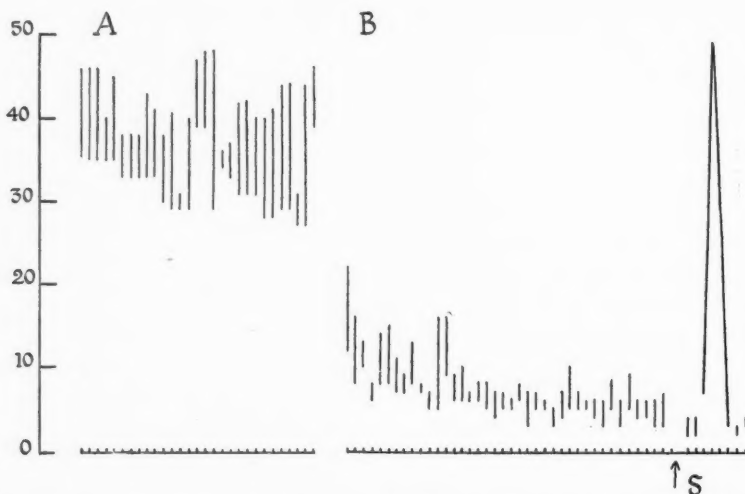


FIG. 6. Case II. A. June 10, 1921. Some pain felt in mid-line just below and also 5 cm. above level of bag, which was situated in lower end of oesophagus. B. June 23, 1921. No pain. The arrow indicates where some of the tracing has been omitted. s is a swallow.

On June 8 he was examined with the bag in the lower end of the oesophagus at 2.30 p.m., $2\frac{1}{2}$ hours after having partaken of a big dinner. His pain was situated just at the level of the bag, and showed no gradation in intensity. The painful spot was tender on pinching up the skin, over about an area of 1 inch in diameter. The bulb was then passed into the stomach and a record was obtained with it just immersed beneath the level of the fluid. A perfectly normal result was obtained. The oesophageal tracing on June 8 (not reproduced) resembled that of the previous case. The mean pressure in the oesophagus was 21 cm. and there were superadded intermittent contractions with increase of pressure to +34 or +38 cm. On June 13 he noticed slight 'heaviness' but no pain, and the heaviness was situated lower down, 3 inches above the umbilicus, and was probably not connected with the oesophagus. The mean pressure was 6-7 cm., which is normal, and the excursions were much less, the maximum pressure being 16 cm. As in Case II, a swallow produced a maximal contraction of 42 cm. pressure.

Case IV. Emma Cr., aged 44 years, married. Colectomy was performed in 1915 for constipation. Since the operation she had still to take Seidlitz powders.

Pain 2 hours after meals was noticed in 1919. It had been much worse lately, and she had vomited, the vomit being streaked with blood. Admitted July 3, 1921. X-ray—some gastropnoxis; greater curvature 3 inches below iliac crest. Tenderness over duodenum, which could not be seen even after manipulation. A little delay in emptying of the stomach. Faeces contained occult blood and gave a haematoporphyrin spectrum. Fractional test-meal normal. Diagnosis, ulcer, ? duodenal. Subsequent history: a chronic gastric ulcer was excised at the end of 1922.

The patient was examined on July 14, 1921. The bulb was situated 5 cm. above the dome of the right diaphragm. The mean pressure was 8 to 10 cm. It is quite likely that if it had been placed rather lower in the oesophagus the mean pressure would have been higher. The seat of the pain, which corresponded to the lower end of the oesophagus, was situated 3 cm. below the dome of the right diaphragm. She also had pain 3 inches lower still; this probably originated in the stomach, but it was not investigated. There were large contractions of the oesophagus at rather irregular intervals, but on the average once every 13 seconds, and the exacerbations of the pain corresponded roughly with the increase in activity of the oesophagus. A pressure of between 30 and 40 cm. was recorded 22 times in 3½ minutes.

Case V. C. P. Ch., aged 32, engineer. In May 1921 he complained of pain behind the sternum, coming on about half an hour after meals. It became better after eructation. This gave place to a feeling of 'stoppage' behind the sternum, which was relieved by eating, and was noticed again half an hour later. The associated pain was not so bad as the one previously complained of. X-ray showed a spasm in the oesophagus at the top of the sternum. This disappeared at once after swallowing some barium. The stomach was normal and the motility of the organ was satisfactory.

The bag was introduced into the upper part of the oesophagus. The mean pressure was 7-8.5 cm., which is high for this position in the oesophagus. Contractions due to swallowing movements took place about every minute, producing a pressure of 18 cm. Moderate pain was felt. At the end of nearly 4 minutes the pain became very severe. The mean pressure rose to 15 cm. and more. The number of contractions increased to about 1 every 15 seconds, and pressures of 26, 29, and 47 cm. were recorded. Many swallowing movements were noticed in this period.

Case VI. Annie Wal., married. In the summer of 1920 she was in hospital for a gastric ulcer. A small niche was observed by X-rays rather high up on the lesser curvature. She improved with rest and dieting and was discharged. The symptoms reappeared on October 23, and the niche was seen again. Her symptoms again disappeared. Diagnosis, chronic gastric ulcer.

About a year later she noticed some pain just inside the apex-beat at the inner side of the 5th space. It was thought that this might be from the oesophagus, and so she was examined with the bag. At the date of the examination the pain itself had disappeared for a week, though she was still tender over the spot. The tracing showed that the mean pressure in the oesophagus at the level of the tender spot was high, varying from 15 to 21 cm. Corresponding to an indigestion pain, which was suddenly noticed for a short time, there were increased contractions and a pressure of over 30 cm. was registered in a quarter of a minute. The pressure then fell back to the previous level. The bag was kept in over half an hour. There was no tendency shown for the mean pressure to fall any lower than 12 cm. all the time the observations were made; and this relatively high pressure can be correlated with the feeling of tenderness and the pain she had previously noticed.

From these cases it may be considered that pain in the upper part of the

epigastrium and beneath the sternum and its neighbourhood, often called 'heart-burn', is due to events in the oesophagus.

The following case is added to show that angina pectoris has no relation to the oesophagus:

Case VIa. E. T. K., aged 42, farmer. For some years he had complained of pain in the upper part of the chest on the left side, after exertion. It used to pass down the left arm. He was a stout man of exemplary habits. There was no history of alcohol. X-ray showed that the heart was greatly enlarged to the left side, and the stomach seemed somewhat displaced to the right. There was no valvular disease.

An oesophageal tracing was taken. The bag was 3 cm. above the dome of the right diaphragm. The mean pressure was 1 cm. falling to 0. The patient then took some exercise, and slight pain followed. The oesophageal tracing is not shown. The mean pressure had fallen to -1 cm. and there were still no contractions. It was noticed that swallowing produced very little effect on two occasions; but on another occasion, after swallowing, a rise of 10 cm. pressure was observed.

The stomach record was also taken. The mean pressure was +8 cm., which is normal. The record was not taken when he had pain; but in another patient who had mild anginal attacks after exercise it was observed that the attack was cut short by the patient sucking air into the stomach, so that the gastric air-bubble was seen on the screen to increase in size. The case is mentioned because Verdon (17) has claimed that angina pectoris is a gastric disorder and due to distension of the stomach. We regard it as primarily a disease of the circulation.

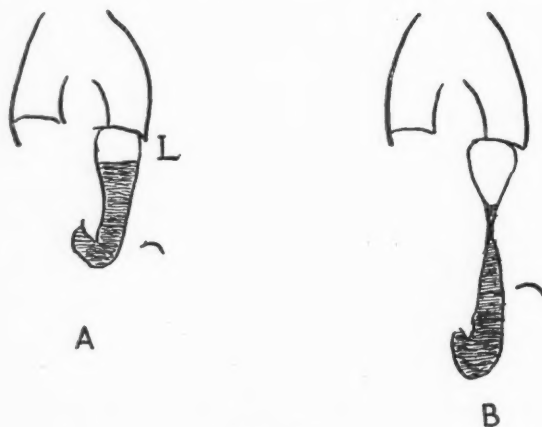


FIG. 7.

The Stomach.

When the pressure inside the normal stomach is considered, the fact that it normally contains some liquid, at any rate during the day-time, must be taken into account. The liquid has a horizontal upper level that may often be seen by X-rays in the upper part of the body of the stomach, if the latter is pretty full, beneath the bubble of air, which occupies the fundus (see Fig. 7, A). Now

it is clear that if the bulb is lying vertically in the fluid of the particular stomach shown at A, it can make no difference to the manometer reading, at whatever level the bulb is situated, provided it is entirely immersed. We have often verified this. In other words, the pressure at any point in the liquid is the pressure at L + the height of liquid between L and the particular point investigated. The important thing is to find what the pressure at L really is. This is obtained by marking the level of liquid in the stomach on the body, from X-ray observations, and measuring the height of the manometer above it. We assume that the liquid in the stomach has about the same density as water. We have always made our measurements in this way, and when the stomach has not had much fluid in it we have often asked the subject to drink some water.

We have found that the pressure measured in this way usually varies within quite narrow limits (5-11 cm.), as the table shows; provided the subject is standing quietly in the vertical position. The pressure in the stomach will be found to rise considerably if the patient contracts his abdominal muscles, or if the abdomen is pressed. There is a slight respiratory variation of one or two centimetres, the pressure rising during inspiration, while in the oesophagus the pressure falls during inspiration as would be expected.

Table showing Pressures in the Upper Part of the Stomach, measured from the Upper Horizontal Level of Liquid in it.

	Pressure, cms. of Water.
E. P. P. Normal	9-10
W. W. P. Normal	6-7
Wm. Pw. Gastropnoia	6-11
James We. Hypertonic stomach, duodenal ulcer	6-8
Peter Fre. Gastric ulcer, gastro-jejunosomy	6-8
Dan K. Dyspepsia, ? ulcer	5 *
Charles F. Old appendicitis, dyspepsia, some gastropnoia	6-8
Timothy O'Ke. Carcinoma ventriculi	9-10
E. T. K. Angina pectoris	9
Leslie Wil. Duodenal ulcer	7-8
Mary Cl. Gastric ulcer, gastro-jejunosomy	7-10
Joseph Ch. Duodenal ulcer, hypertonic stomach	6-10

* 13 cm. after taking sodium bicarbonate and citric acid.

The pressure in the stomach was raised from 5 cm. to 13 cm. in the case of Dan K., after taking separately a dose of sodium bicarbonate and citric acid, enough to produce 500 c.c. CO₂. This rise occurred just before the gas was eructated.

We have noticed a rise from 7 cm. to 15 cm. in Case IX, also just before an eructation, when no pain was experienced at all. This patient was a stoker, aged 51, with carcinoma ventriculi which was confirmed by operation.

The intragastric pressure measured in this way represents the pressure in the fundus and body of the stomach, but not necessarily that in the pyloric part of the stomach. The fundus and body of the stomach play the part of a reservoir for food, and the walls remain for the most part inactive, while the pyloric part acts like a mill, as Cannon has pointed out, so that the food in this portion is mixed up and passed on to the duodenum by peristaltic action. We should expect to find very different pressure relations in these two parts of the stomach during peristalsis, and this is in fact found to be the case.

We have records of such differences from Wm. Pw. (Case I). He had gastroptosis, and a diagram of his stomach is shown diagrammatically at Fig. 7, B, as indicated by X-rays. The stomach was dropped, so that the lowest part of the greater curvature lay 7 cm. below the highest point of the iliac crest. The walls sagged together in the middle of the stomach when the patient was standing vertically, and so the stomach was virtually separated into two compartments. He was examined on May 10, 1921, wearing his Curtiss belt. The bag was placed at the bottom of the lower compartment, about 16 cm. below the level of fluid in the stomach. The pressure remained very constant and there was only a respiratory excursion of 1 cm. Taking the level of fluid in the upper compartment as the zero in this experiment, the mean pressure in the lower compartment was -3 to -2 cm. On raising the bag into the upper compartment the pressure was found to rise to from $+5$ to $+7$ cm., the same fluid level being taken as the zero, and the respiratory oscillations were increased to about 3 cm.

In the two other cases of gastroptosis which we have examined, we have noticed the same rise of pressure on passing from the lower to the upper compartment, when the walls sagged together, and we believe as a general rule that in gastroptosis there is a difference of pressure in the upper and lower parts of the stomach, though we are not at present prepared to express an opinion as to what the significance of this really is. In one case the wearing of a belt increased the pressure of the lower compartment until it was the same as that in the upper part of the stomach.

After taking these tracings, the patient's belt was removed, and he noticed the occurrence of slight pain after a short time. A tracing in the lower compartment showed that the mean pressure was even lower than before, viz. 6 or 7 cm. below the zero mark. The respiratory excursions were greater, viz. 2 or 3 cms., and about every 20 seconds there were comparatively large excursions of the manometer. Examination by X-rays showed that these latter were due to peristaltic contractions. The wave was seen to travel round the lowest part of the greater curvature from left to right. The highest point of the manometer was noticed to coincide with the middle position of the wave, in which the indentation was at a maximum. The relation of the slight pain to the intra-gastric pressure was also observed. There was no relation to the individual peristaltic contractions; but it was noticed that the presence of the pain coincided roughly with an increase in the mean pressure of the lower part of the stomach to -3 or -4 cm. The bag was then raised into the upper compartment and a tracing was obtained very similar to the previous one, though the mean pressure was slightly greater, viz. 8-10 cm. The effect of the peristalsis in the lower part of the stomach was not shown at all in this tracing of the upper part of the stomach.

Case VII. Charles F., aged 59, a skin drummer. History of syphilis in 1884. He had abdominal pain two years before and for the last five weeks. Admitted August 10, 1921. Two fractional test-meals showed hypochlorhydria. There was no occult blood in faeces. X-ray showed some gastroptosis, with tenderness over the pyloric region. A laparotomy was performed. It was found that the stomach and duodenum were quite normal. The tail of the pancreas was rather freely movable. The appendix was absent and only the stump was left, and the part round was rather adherent. He had had no previous operation and it was suggested that the appendix had sloughed off on some previous occasion.

The patient was investigated on October 10, 1921. A spherical bag was used instead of the finger-stall. Its capacity was about 45 c.c.

A tracing taken with the bag in the lower part of the stomach showed a rise in the mean pressure and in the height of the contractions when the pain was bad. With little pain the mean pressure was 7-9 cm., with much pain the mean pressure was 11 cm., and contractions caused increases of 3 to 5 cm. The

pain was felt 2 cm. above the bag. A tracing was also taken with the bag in the upper part of the stomach.

There was very much less correspondence here between the pressure changes and the pain, and what correspondence there was can probably be explained by the transmission of the pressure changes from the lower to the upper part of the stomach.

Case VIII. Beatrice Joh., aged 35, married, came up to the hospital deeply jaundiced, with severe epigastric pain. She had had haematemesis. She was admitted to hospital, and after a few days the jaundice cleared up and she passed a large gall-stone per rectum.

She was examined with the finger-stall bag during the afternoon following admission. The pain had then largely subsided. The bag was in the stomach, but as X-rays were not used it was impossible to determine its position. It was passed as far as possible and so was probably at the lower end. During the pain the intragastric pressure was observed to be 2 or 3 cm. higher than when the pain was absent. This case is interesting as it shows that the epigastric pain felt in a case of gall-stones was due to events occurring in the stomach. Presumably the contractions were reflex in origin.

Duodenum and Jejunum.

With observations on pressure changes in the duodenum and jejunum, it is necessary to consider what base-line to use, from which to measure the pressure. Conditions are quite different from the stomach, which contains a column of liquid, so that the pressure should obviously be measured from the surface of the liquid, if the bag is immersed in it. The small intestine is shut off most of the time from the stomach; it is in a more or less collapsed condition and contains a mixture of liquid and gas in variable proportions. It would be quite wrong to measure the pressure from the surface of the liquid in the stomach. The pressure in the intestine, as in the oesophagus, can only mean the head of the column of fluid that is supported by the walls of the intestine at the point where the bag is. Consequently, we have always taken the precaution to mark exactly on the surface of the body the level of the bag, and have measured the height of the manometer above this.

Most of our observations on the duodenum and jejunum have been carried out on three patients, and as we have also examined the stomach and oesophagus in these patients, their detailed consideration will be left till the end. We have, however, examined one patient who may be regarded as a normal.

Case X. T. Lew. Two or three months previously (December 10, 1920) he had come up to Out-patients complaining of severe dyspeptic symptoms. X-ray examination showed the presence of a hypertonic and rapidly emptying stomach. The greater curvature was $1\frac{1}{2}$ inches above iliac crest. With rest and medical treatment the symptoms completely disappeared. X-ray on this occasion (April 7, 1921) showed that the stomach was perfectly normal in size, position, and motility. He had had no pain for some weeks. The duodenal mean pressure was 14 cm. Rises of pressure of 2 or 3 cm. were probably due to respiration. Rises of 4-6 cm., which were also seen in the tracing, were probably the result of slight contractions.

The following three cases are of interest, as they were examined on many occasions, and records were taken in several different parts of the upper alimentary tract.

Case XI. Peter Fre., aged 63, labourer. He had gastric ulcer in 1919, and gastrojejunostomy was performed. This relieved him of his symptoms for about two years. He then noticed that pain returned. He was operated on again in 1920, and an ulcer was found on the lesser curvature adherent to the liver. The stomach was opened and the ulcer cauterized. He did not obtain any relief.

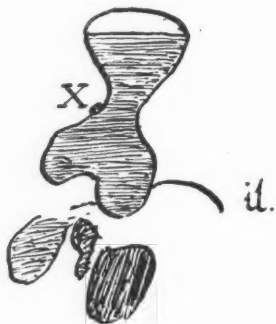


FIG. 8.

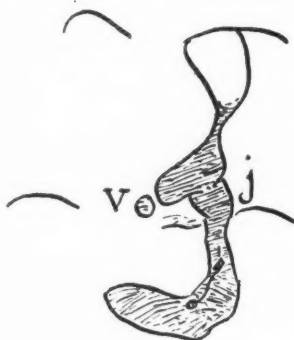


FIG. 9.

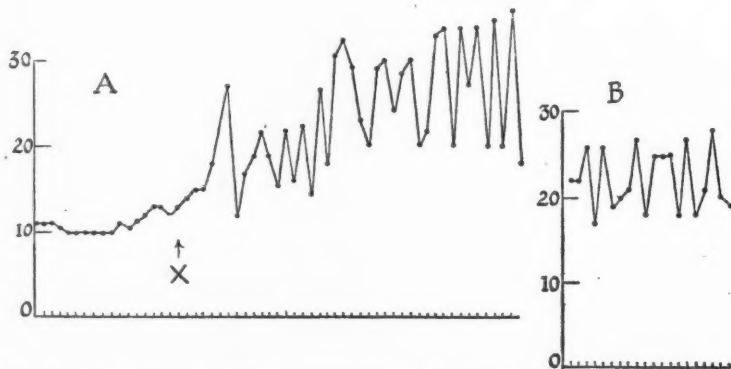


FIG. 10. Case XI. A. Bag in stoma and jejunum. B. Bag lower down in jejunum. Time, 5" intervals. At x, the pain experienced, which up to that time had been slight, suddenly became severe.

Severe pain had continued off and on since then. He noticed this in the epigastrium high up, and also in the abdomen. He vomited sometimes and complained of flatulence. X-ray showed that the gastrojejunostomy opening functions. The barium passed through immediately. A niche, representing the ulcer, was seen on the lesser curvature of the stomach, opposite the stoma. The stomach was often over-distended with air, and there is no doubt he had much aerophagy. He was constipated. The fractional test-meal contained free HCl and the samples were mostly bile-stained. No remedial treatment seemed to be of any use in preventing the attacks of pain from coming on. On November 14, 1921, he had jaundice, which lasted about three weeks.

Subsequent history: Operation was performed by Mr. E. C. Hughes, in the summer of 1922, and a small non-adherent ulcer on the lesser curvature of the stomach was excised, and a small gastrostomy opening made which closed up in a few weeks. He was discharged relieved from his symptoms. The symptoms recurred subsequently

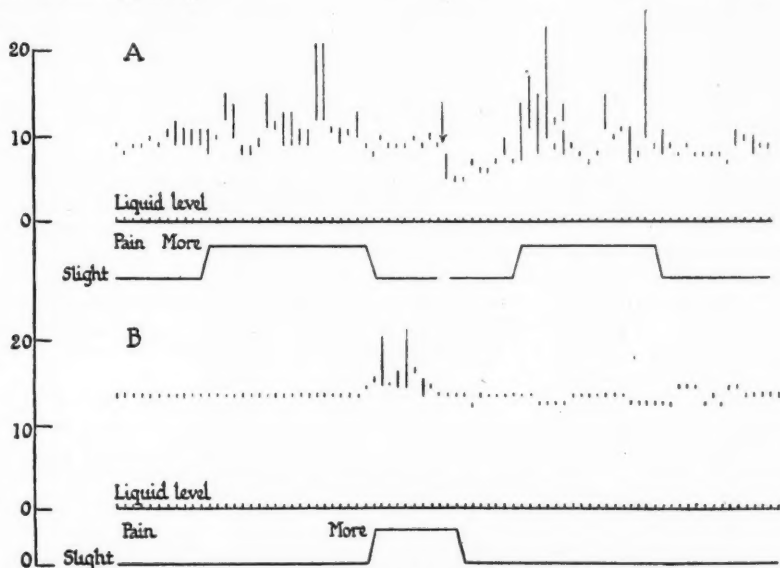


FIG. 11. Case XI. A. Bag in pyloric part of stomach. At the arrow in the middle of the tracing a part of the tracing lasting for 9 minutes is omitted, where the pain and the alterations in pressure were slight. B. Bag in pyloric part of stomach and stoma. Time intervals $7\frac{1}{2}$ secs.

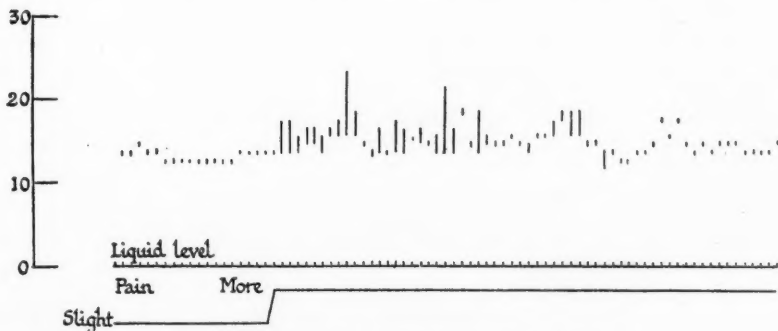


FIG. 12. Case XI. Continuation of Fig. 11, B.

The X-ray appearance of the stomach (November 15, 1920) is seen in Fig. 8. The position of the ulcer is marked with x. The entrance to the jejunum is distended with barium, and coils of intestine lower down also contain barium. The right iliac crest is marked *il*. Fig. 9 shows the stomach on March 17, 1921, with less food in it. The junction of stomach and jejunum is well seen (*j*). These drawings are accurately reduced to scale.

A tracing was taken from the oesophagus with the bag $4\frac{1}{2}$ cm. above the level of the right diaphragm. One hour earlier he had been writhing about

upstairs in bed with the most severe pain, which was relieved on vomiting a little phlegm. During examination he noticed very little pain, and what there was was situated 6 cm. below the bag. The tracing was quite a normal one, and the strong contraction after swallowing, causing the pressure to rise to 38 cm., was also quite normal. The mean pressure was 1-3 cm. The bag was then passed into the stomach, and lay $2\frac{1}{2}$ cm. beneath the level of the liquid. Quite a normal record was obtained. The mean pressure was 6 cm. An oesophageal tracing, taken two days later, afforded a marked contrast. The bag was 3 cm. above the right diaphragm and the mean pressure was about 3 cm., when there was slight pain only. When the pain was more, contractions of the oesophagus were observed, the pressure rising to 17 and 27 cm.

In another experiment the bag was in the stomach. The mean pressure was at first 8 cm. This was probably a little too high, because the bag was not beneath the liquid, and so the base-line should be 2 or 3 cm. higher. Later, he had very severe pain. The tracing was a contrast to the previous one, showing variations in pressure up to 14 cm. These changes are not very great. This is no doubt because the fundus was not itself contracting, and the variations in pressure were due to severe contractions in the lower part of the stomach, causing a rise in the general pressure of the organ. His bodily movements, owing to the pain, were not sufficient to cause any appreciable alteration in the intragastric pressure.

The bag was then allowed to fall into the lower part of the stomach above the stoma. The pain had become much less by this time. The mean pressure was 5 cm., measured from the liquid level. Groups of contractions appeared at intervals, causing the pressure to rise to 9 cm.; possibly these were peristaltic in nature. But there were none of the violent contractions recorded in this part of the stomach on other occasions.

Fig 10, A, shows the contractions observed with the bag in the stoma and jejunum. It was hanging vertically with the middle of the bag 1 inch below the umbilicus. The mean pressure, taking the position of the bag as zero, was 10 cm., and the maximum 30 cm., and more, when he had severe pain. At the end of the experiment it was noticed that the bag had fallen 6 cm. and was lying horizontally, in a loop of the jejunum. The base-line had thus altered. The jejunal contractions are shown at B. It is to be noticed that during the contractions the mean pressure had risen considerably, to 18 or 20 cm. of water. Pain was felt all the time in the epigastric angle, which was rather higher than the part that was being investigated.

Fig. 11, A, shows a tracing in the pyloric part of the stomach. The pain was felt $3\frac{1}{2}$ cm. above the level of the bag in the middle line and also passed upwards into the epigastric angle. This tracing, which shows the contractions associated with the increase of pain, was taken before his dinner. At B the tracing taken after dinner is shown, and this is continued straight on in Fig. 12. At the end it was found that the end of the bulb had slipped and was projecting into the stoma. This probably happened while he was having dinner. The bulb was kept down all through the meal.

This patient's pain was associated, at varying times, with contraction in the oesophagus, pyloric part of the stomach, and jejunum.

Case XII. Mary Mas., aged 47, married. She had a pain with haematemesis for three months when she was 14 years old, and again when 27, during her first pregnancy, and also during three months when she was 29. She had intermittent attacks during the next four years, i.e. till 1907, when she had rheumatic fever. She was then better till 1914, but had operations for strangulated hernia in 1911, and for appendicitis a year later, when a gangrenous appendix was removed. In 1914 she had pains and haematemesis, and an operation was performed, but no ulcer or sign of healed ulcer was found, so nothing was done. Test-meal showed no hyperchlorhydria. Patient was diagnosed as gastrostaxis.

She was better till 1920, when she had pain and haematemesis again. X-ray showed tenderness at the pylorus, but no deformity could be definitely made out. A fractional test-meal on two occasions showed absence of free HCl. Her pain was made worse by taking dilute hydrochloric acid (B.P.) with meals in doses of 50 minims. It was thought that in the past she had suffered from attacks of acute ulcer or haemorrhagic erosion, and that, considering the length of her recent history, one of these acute ulcers might have become chronic, and so operation was again advised and carried out early in 1922. Adhesions were found round the pylorus, but there was no evidence of ulcer in the duodenum and stomach, and no abnormality elsewhere in the abdomen.

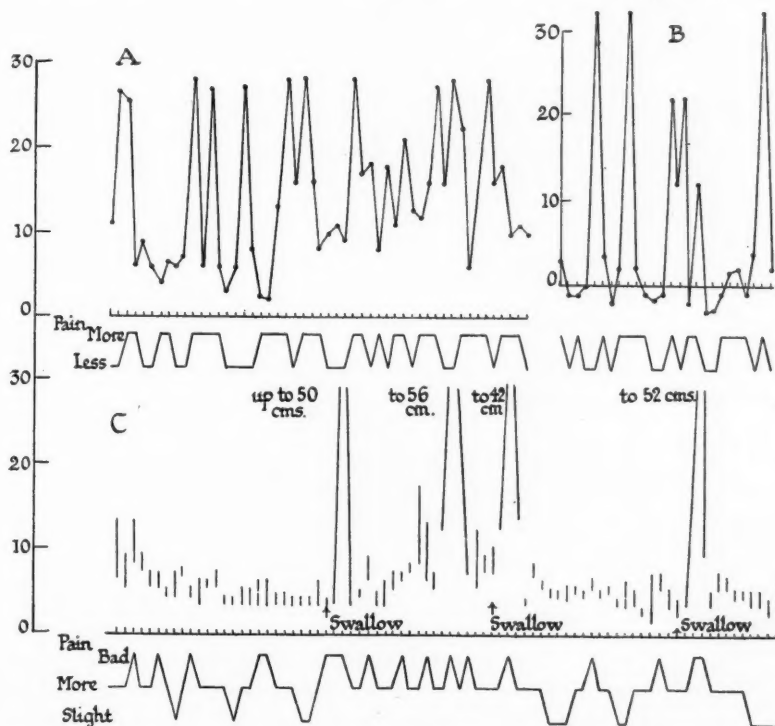


FIG. 13. Case XII. A. Bag in lower end of oesophagus. B. Bag in middle of oesophagus. Time in 5" intervals. C. Bag in lower end of oesophagus. Time in 7½" intervals.

She was examined with the bag in the oesophagus on May 27, 1921 (Fig. 13, A). The pain was felt in the epigastrium on the right side rather high up and against the right costal margin, and the bag was 5 cm. above the level of the right diaphragm. The mean pressure varied between about +2 and +8 cm. There were numerous large contractions which raised the pressure 28 cm., and these corresponded roughly with increase in the pain. Similar contractions were seen when the bag was situated in the middle part of the oesophagus. The mean pressure varied from -2 to -4 cm.

The patient was re-examined in November 1921. She complained of pain at about the same situation as last time. It was noted as being 4 cm. below the level of the right dome of the diaphragm, 14 cm. above the umbilicus, and against the right costal margin. She said it was not so bad as the last time.

The bag was placed on a level with the right diaphragm and was seen to descend and approach the stomach during contraction of the oesophagus. The mean pressure was 3.5 to 5.5 cm. Three swallows were noted and corresponded to very pronounced contractions of the oesophagus, with rise of pressure to 50 cm. On the whole the oesophagus was much less active than last time, although most of the peaks in the pain record corresponded to some rise of pressure. Some definitely increased activity was shown in the middle of the tracing when the pain was continually becoming bad. The mean pressure rose here and the contractions were larger. It seems reasonable to attribute the lessened activity of the oesophagus on this occasion to the fact that she stated the pain was on the whole less than previously.

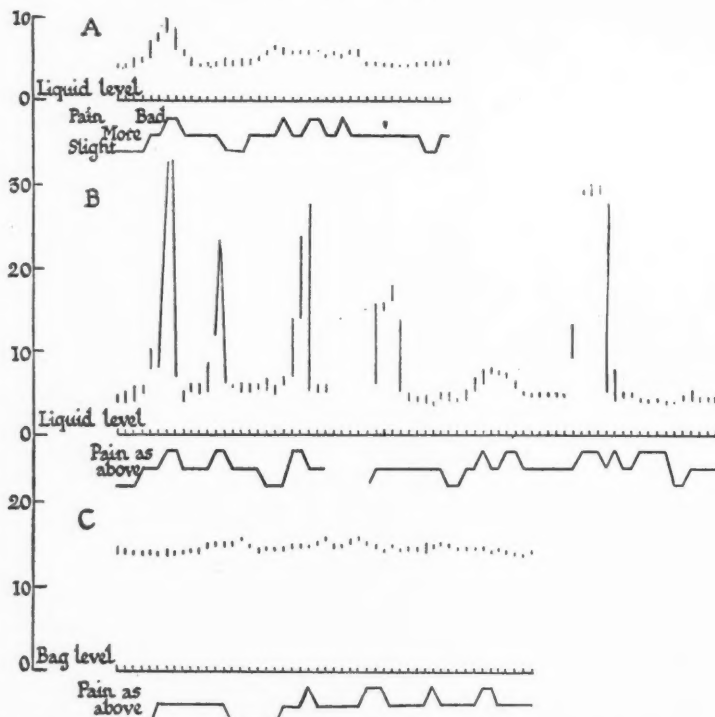


FIG. 14. Case XII. A. Bag in upper part of stomach. B. Bag in pyloric part of stomach. C. Bag in jejunum. Time in $7\frac{1}{2}$ " intervals.

The bag was then passed into the stomach and hung 2 cm. beneath the level of liquid in the body of the stomach (Fig. 14, A). The mean pressure was 4 cm., and there was a definite tendency to a rise of pressure when the pain was bad. This may be explained, as in the case of Peter Fre., by the effect produced by contractions in the pyloric part of the stomach on the intragastric pressure of the fundus. The bag was then passed into the pyloric part of the stomach as near the pylorus as possible. It lay $1\frac{1}{2}$ inches above, and to the right of the umbilicus. At the end of the observations it was noticed to be 2 cm. lower and rather nearer the middle line.

The tracing shown at B (Fig. 14) is in marked contrast to that obtained from the body of the stomach. Very strong contractions were obtained, and these corresponded very closely to the periods when the pain was worst. There can

be little doubt that the pain in this case was associated with contractions both in the oesophagus and in the pyloric part of the stomach, and on this occasion the pyloric contractions were more striking than those seen in the oesophagus.

On the next day the bag was passed through the duodenum and over the duodeno-jejunal flexure and into the jejunum. The mean pressure on the bag was 14 cm. The latter was situated 15 cm. below the level of liquid in the stomach and 6 cm. below the bottom of the stomach. No doubt the relatively high pressure of 14 cm. was due partly to the pressure exerted by the upper abdominal viscera on the jejunum at the point. It is obvious from c (Fig. 14) that there were no jejunal contractions associated with the pain, but the pain was less than on the previous day. The attempt to find out whether there were duodenal contractions failed in this case because, on withdrawing the bag, it slipped back rapidly into the stomach.



FIG. 15. Case XIII. X-ray tracing with bag in stomach.



FIG. 16. Case XIII. June 29, 1921, 2.45 p.m. X-ray tracing of stomach with bag in duodenum.

Case XIII. Joseph Ch., aged 42, printer's warehouseman. He has always been subject to attacks of vomiting and headache. Severe epigastric pain was first noticed five years before, coming on $1\frac{1}{2}$ hours after food and accompanied by headache. Admitted to hospital February 27, 1921. X-ray showed small raised hypertonic stomach which was empty in $1\frac{1}{2}$ hours. There was tenderness at pylorus and slight irregularity was seen at the top of the duodenal cap. Fractional test-meal showed hyperchlorhydria with highly acid resting juice. Faeces gave a positive guiac test for occult blood, and a haemato-porphyrin spectrum was seen. Diagnosis, duodenal ulcer.

Two diagrams of the stomach drawn to scale are shown in Figs. 15 and 16. The greater curvature is well above the iliac crests and umbilicus. In Fig. 15 the bag, with its two opacities at top and bottom, is shown in the stomach, and in Fig. 16 the bag is shown at about the junction of the second and third parts of the duodenum.

This patient was especially liable to 'hunger pains'. These were experienced some two or three hours after food and were relieved by taking food.

A set of observations is shown in Fig. 17 with the bag in the stomach situated 7 cm. below the level of the liquid. These were taken at 11.15 a.m. and he had had no breakfast. He noticed a regular gradation of sensations. At one time there would be no pain, then the pain would be slight, then more, and finally an eructation might occur, and immediately after this the pain would disappear for about 15 seconds. Corresponding with these sensations there are rises of pressure. The highest pressure was usually obtained just before the eructation, but when the sensations were less they were still accompanied by a contraction of the stomach with a rise of pressure.

We obtained this type of curve on many different occasions in this patient, and it always showed the same characters. Sometimes eructations were more

frequent. As already pointed out, only the highest points registered by the manometer are recorded in Fig. 17. As a matter of fact there were rapid oscillations backwards and forwards, and these are seen better in Fig. 18, where the minimum readings as well as the maximum readings were recorded, so that an idea is obtained of the range of oscillations.

After the observations in Fig. 17, A, the patient had his dinner, and was examined again at 2.45 p.m. The bag was again passed into the stomach, 11 cm. below the surface of the liquid—rather lower than before. He felt quite comfortable and there were no sensations. The pressure-curve (see Fig. 17, B) offers a great contrast to the preceding one. The pressure only varied by 3 or 4 cm.

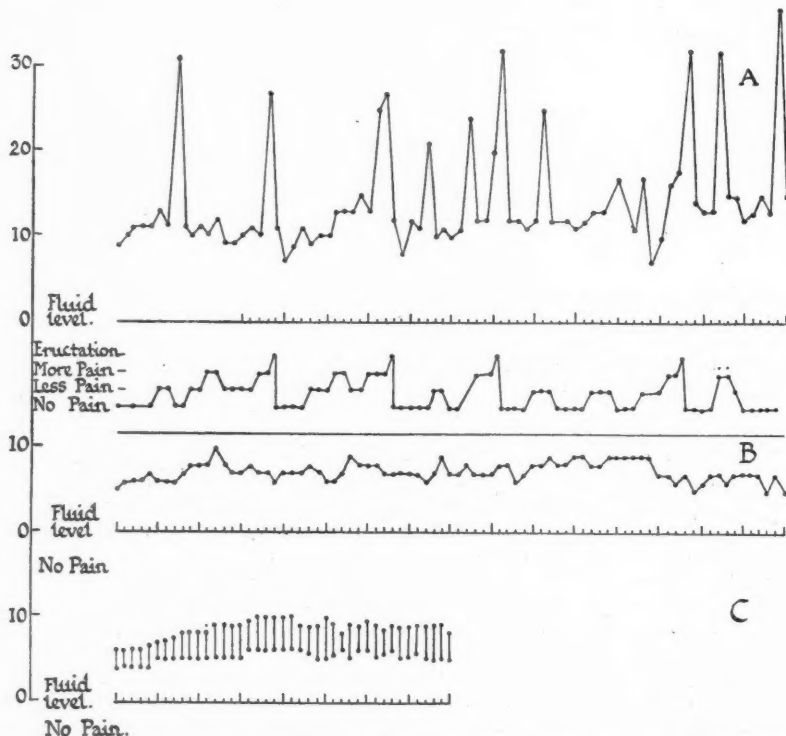


FIG. 17. Case XIII. A. Bag in stomach with various degrees of pain. B. Bag in stomach with no pain. C. Bag in stomach with no pain. Time in 5" intervals.

Fig. 17, c, shows another record obtained in the stomach, when no pain was experienced. The oscillations are purely respiratory and the stomach did not show any of the contractions associated with pain.

Fig. 18 shows a record with the bag in the duodenum. The mean pressure was about 18 cm. This record is comparable to Fig. 17, A, but the contractions have been recorded in the other way. A rise in pressure occurs as the pain becomes worse, and the highest value is obtained just before an eructation, and falls back to the mean pressure immediately afterwards.

When these observations were made, the possibility of oesophageal contractions had not been realized, and so no observations on the oesophagus were carried out at the time. However, the oesophagus was examined an hour after dinner on June 29. No pain was experienced. The bag was situated about

3 cm. above the right diaphragm. A level record was obtained at about 6 cm. mean pressure. There was a strong contraction after a swallow, with rise of pressure to 35 cm. Just before the end of the record another strong contraction to 37 cm. was observed. This was not due to swallowing, because there was no movement of the thyroid cartilage. The patient also said he did not swallow, but he felt a sensation round about the umbilicus as if 'wind wanted to come up, but was pushed down instead'. From this single observation we have very

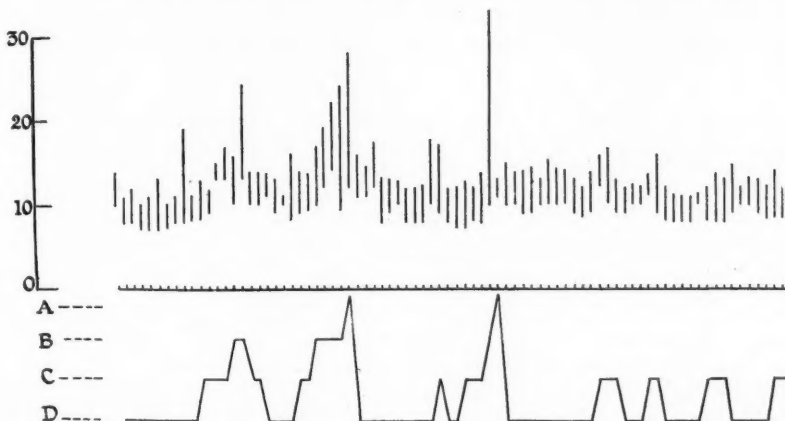


FIG. 18. Case XIII. Bag in duodenum. The level of the liquid in the stomach is taken as zero. The level of the bag was 10 cm. lower. Time in 5" intervals. A. Eructation. B. Severe pain. C. Slight pain. D. No pain.

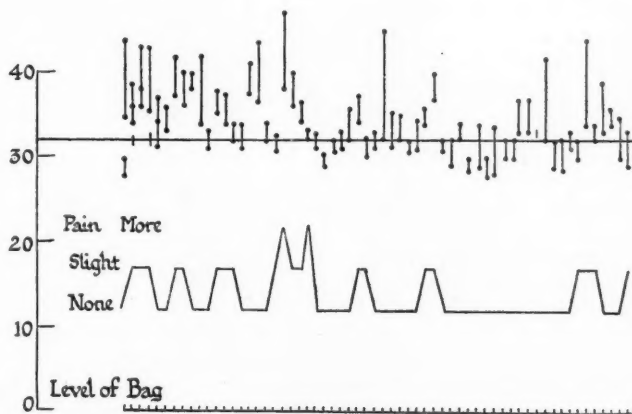


FIG. 19. Case XIII. Duodenum. Time, 7½" intervals.

little doubt some movements of the oesophagus occurred in the patient corresponding with the movements in the stomach and duodenum, and this high contraction accompanying the desire to eructate is very suggestive of the anti-regurgitation reflex already described.

The bag was then passed into the duodenum and was seen lying horizontally at about the level of the umbilicus in the second or third part. The record in Fig. 19 was obtained. He was noticing at the time slight pains with a feeling of 'wind' low down round the umbilicus which had just appeared. This tracing

is quite characteristic of the other records already shown, and need not be described further. It is, however, worth noting that there were no eructations. The larger contractions were associated with increase of pain.

Contractions of the stomach and duodenum were present simultaneously in the patient when he had pain and feelings leading to eructation. This was shown on several occasions by withdrawing the bag from the duodenum into the stomach and noticing similar contractions in both places.

We thought it important to find out if possible what relation there was between these two sets of contractions. The patient already had one bag in the duodenum during the last set of observations. He took another similar bag which was kept in the stomach. We attached the manometer belonging to the duodenal bag on to a piston recorder, and the other manometer on to a Marey's tambour, and recorded the excursions on a kymograph. In the tracings (Plate 3, Figs. 20 and 21) the upper curve is from the duodenum, the middle curve from the stomach. The variations in the latter are small because the Marey tambour produced a smaller excursion than the piston recorder. These curves do not in any sense represent changes of pressure in absolute value. Pain is represented underneath by a fall in the lever, and below this the time is marked in seconds.

The small waves in the stomach and duodenum, best seen in Fig. 21, are respiratory, and were seen to occur simultaneously on the tracing when the kymograph was travelling faster. On the other hand, the longer waves which were due to contractions did not coincide exactly. The stomach wave was one second in front of the duodenal wave.

We are not prepared at present to explain this small difference. Peristalsis as seen in the stomach filled with an opaque meal is slow and deliberate, and it would certainly take more than a second for such a wave to pass right along the stomach as far as the second part of the duodenum.

At the same time it is difficult to imagine that these contractions found so constantly in the stomach and duodenum are not due to a wave conducted rapidly along. We hope to carry out more observations on this point.

The relation of the pain experienced by the patient to the contraction is of great interest. Pain gradually came on while the observations were being made. At first it was a momentary effect, as shown in Fig. 20, associated sometimes with single, sometimes with double and treble, contractions of the stomach and duodenum. The interesting part is that the pain is always signalled just after the contraction is finished. This agrees with what we have found in the oesophagus, when using a distended but collapsible rubber bag containing air. The explanation that we have suggested (12) is that the pain is due to the stretching of the wall of the viscus, and especially its nervous elements, during relaxation of the muscle.

In Fig. 21 the intervals during which pain is experienced are longer, and they are associated with larger numbers of contractions grouped together. Four or five separate contractions forming a group are seen, and in one case there are as many as ten. In the latter case the duration of the pain is correspondingly lengthened. Further, the beginning of the pain does not correspond with the first contraction of the group, but falls perceptibly later. This agrees with our previous finding that pain occurs after the contraction. In the last group of Fig. 21 the pain was not signalled until towards the end of the group of contractions, showing that there was probably some kind of cumulative effect.

At the end of the observations the position of the bag in the duodenum was identified by X-rays. Fig. 16 was drawn after filling the stomach with barium so that the bag could be seen outside the stomach shadow.

The main point of the tracing is that it confirms by graphic means our pressure observations carried out in the X-ray room, which have been fully detailed in the rest of this paper.

Our chief conclusion is that pain in the upper alimentary tract is due to movements either in the oesophagus, stomach, duodenum, or jejunum. We hope to return shortly to the question as to the exact relationship of the pain to the movements, viz. that it occurs usually during relaxation and is abolished by contraction of the visceral wall.

Conclusions.

1. The pressure produced by peristaltic waves in the human oesophagus and their rate of progression have been measured.

2. There is evidence that an oesophageal peristaltic wave ends by causing the cardia to contract, and the cardia descends and probably invaginates itself into the stomach during the process.

3. The 'gastro-oesophageal antiregurgitation reflex' has been substantiated in man.

4. Oesophageal pain or 'heartburn', which is felt beneath the sternum or in the epigastric angle, is associated with peristaltic movements of the oesophagus, and often with a rise in the mean pressure.

5. Anginal pain was in one case not associated with oesophageal movements, and in another case the pain was abolished after sucking air into the stomach. This is contrary to Verdon's hypothesis.

6. The pressure in the stomach, when functioning normally, measures at the level of the liquid between 5 and 11 cm. of water. In gastropptosis the pressure in the upper part of the stomach is higher than in the lower part, and in one case the difference was abolished on wearing a belt.

7. Pain felt in the upper abdomen may be associated with movements in the pyloric part of the stomach, in the duodenum, or in the jejunum (Case XI, subsequent to gastrojejunostomy). There is evidence that these parts may be affected alone or simultaneously, and there may, or may not, be simultaneous movements in the oesophagus, causing heartburn.

8. Some evidence is given that visceral pain may be produced during relaxation of the muscular walls of the viscus.

9. Pressures of over 30 cm. of water may be registered in the stomach just before eructation.

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Case I. Oblique view of oesophagus showing spasm above and below, with air between. The invagination below the upper spasm may be due to a peristaltic wave.

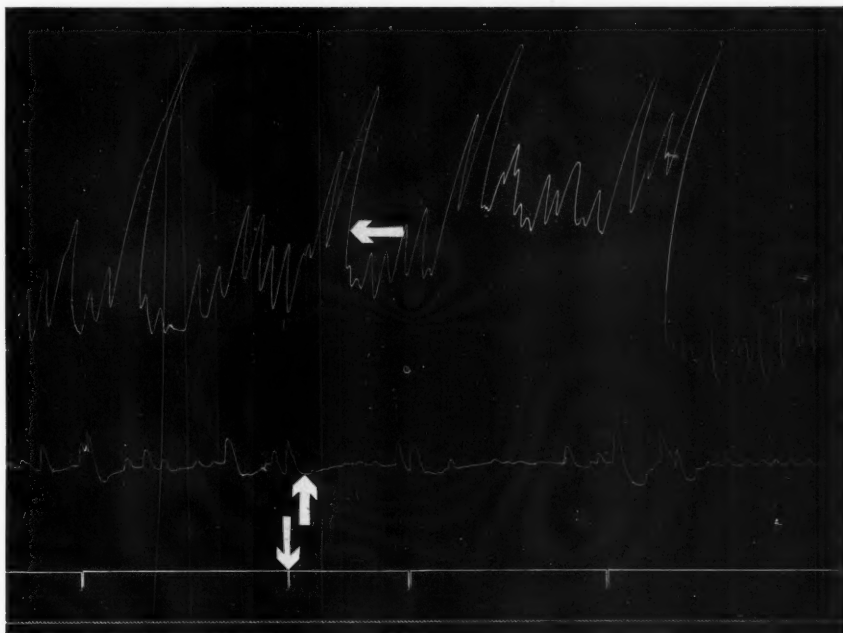


FIG. 20

Case XIII. Upper curve duodenum, middle curve stomach, lower curve pain.
Time in seconds. The arrows mark simultaneous points.

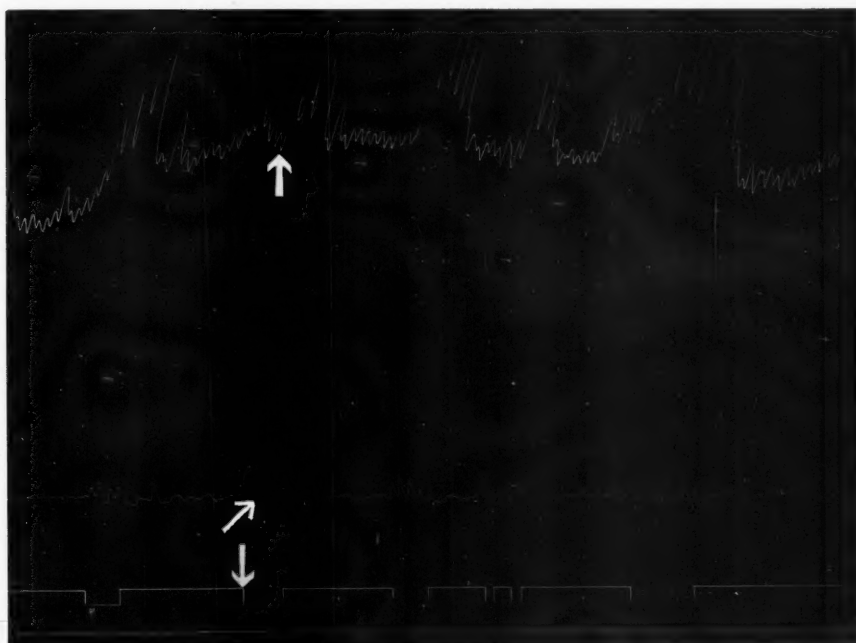
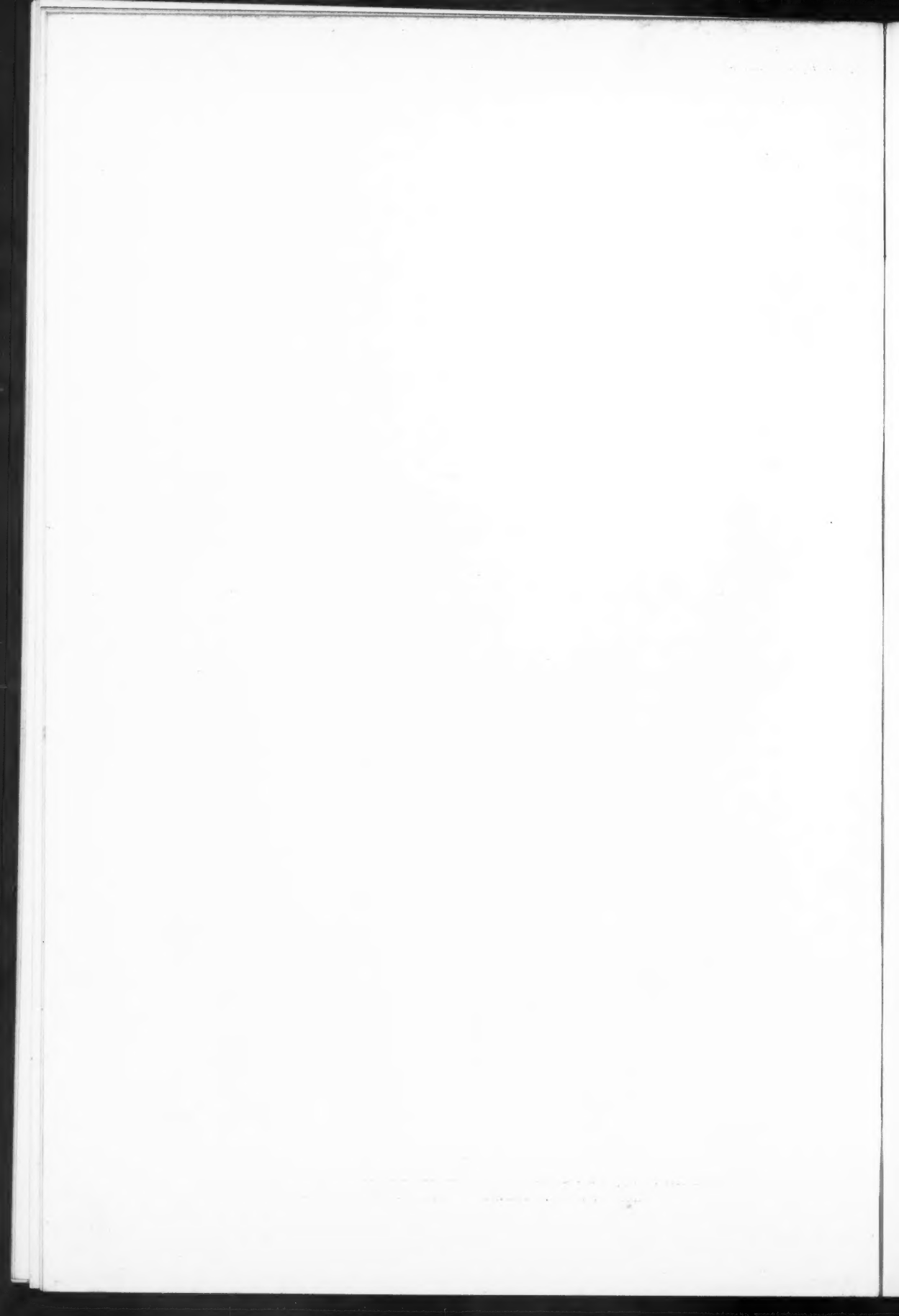


FIG. 20.

Case XIII. Upper curve duodenum, middle curve stomach, lower curve pain.
Time in seconds. The arrows mark simultaneous points.



LIVER ATROPHY

By JAMES MILLER AND ANDREW RUTHERFORD

With Plates 4-8.

Historical.

THE literature of acute and subacute atrophy of the liver may be taken as sufficiently summarized up to 1909 in the papers of Muir (21), Stuart M'Donald (15, 16), Lindsay Milne (12), and Miller (20). The general position at that time was that there were two stages in the disease: first, the so-called 'acute yellow atrophy' with widespread destruction of liver parenchyma; secondly, the 'subacute liver atrophy' characterized by more or less well-marked regenerative changes following widespread initial necroses. To the more prolonged cases of the subacute type where the regenerative proliferation resulted in the formation of tumour-like nodules of liver tissue, the term 'multiple nodular hyperplasia' had been applied by Muir and by Miller, following Orth (22), Marchand (18), and Barbacci (1). Stuart M'Donald and Lindsay Milne (16) in 1909 described five cases of 'subacute liver atrophy', and these writers stated that this condition had been very slightly touched on in literature up to that time, although the cases that had been recorded presented a quite definite train of appearances. They also emphasized the necessity of not confusing such cases with ordinary portal cirrhosis, and among other points of difference referred to the marked interstitial formation of elastic tissue in the latter as contrasted with its relative absence in the subacute liver atrophies.

As regards the nature of the alteration in the liver cell in the acute stage of 'atrophy' the generally accepted view has been that fatty changes play a large part in the stages preceding complete destruction. Stuart M'Donald (15) lays special stress on the essential acute necrosis as distinguishing the change in acute liver atrophy from those commonly met with in delayed chloroform poisoning and in some acute septicaemias. Beattie and Dickson (2), in their *Text-book of Pathology* (1909), agree with this view. Other writers dealing with the subject adhere to the view that fatty changes are predominant.

It has been generally admitted that in the 'restitutio ad integrum' of the liver as a functioning organ the stroma and blood-vessels are supplied by

inflammatory reaction following the destructive change, and that canalization of pre-existing vascular channels may possibly play some part.

There is considerable difference of opinion regarding the mode by which the secreting gland cells regenerate in the cases not speedily fatal. Two possibilities are recognized, the first being regeneration from pre-existing liver cells which survive the general destruction, the second from proliferating bile-ducts. The general consensus of opinion has inclined to the view that the former is the more important of the two. MacCallum (13) laid considerable stress on the latter mode, whilst M'Donald and Lindsay Milne (16) denied it entirely. Minute details of the processes occurring are to be found in the papers of Marchand (18), Muir (21), and Lindsay Milne (12).

The significance of the apparent bile-duct proliferation is variously interpreted. A majority of observers regard it as an active process indicating at least an attempt at regeneration. Mitotic figures have been seen in the cells of these small bile-duct-like structures by several observers. M'Donald and Lindsay Milne (16), and following them apparently Beattie and Dickson (2), take the view that this multiplication is more apparent than real, and that the appearances result from 'a becoming evident of the delicate normal bile-conducting channels which extend between the liver cells and the interlobular bile-ducts'.

An important phase of the reconstruction of the liver following atrophy is the linking up of the new parenchyma with the drainage system of the bile-ducts. This is a matter which does not appear to have received the attention it deserves.

In connexion with aetiology the general view has been that various toxins may be instrumental in bringing about atrophy of the liver: no single well-defined factor having been found to be constantly associated. Within more recent years, however, a number of facts has emerged throwing light upon various problems, especially in regard to aetiology. That acute liver atrophy may complicate or follow syphilis has long been recognized. Braunschweig (3) (1911) stated that about 50 cases of malignant icterus were recorded in syphilis, and of these 10 were in males. Treatment of syphilis by salvarsan, &c., has introduced another factor in aetiology; the supervention of liver atrophy in syphilitics treated by organic arsenic has occurred in several instances. Stuart M'Donald (15) and others (6) (1918) have drawn attention to several syphilis salvarsan cases met with during a very short space of time. There is as yet no agreement as to the exact rôle of the different factors in the causation of those cases. McDonagh (14) is strongly inclined to blame salvarsan or salvarsan plus mercury rather than syphilis alone in these recent cases. He has met with a much greater incidence of liver atrophy in syphilitics treated with salvarsan than in those under the old treatment in former years. On the other hand, isolated cases of cure of advanced syphilitic icterus by salvarsan are recorded (31). Herxheimer (7a), in a recent description (1921) of six new cases of liver atrophy, discusses the whole question of its relationship

to syphilis and salvarsan and of the mode of regeneration of liver tissue. Aetiologically syphilis was a factor in all six cases. He has collected from literature 69 cases in which syphilis was an undoubted factor, salvarsan being excluded and diagnosis confirmed by post-mortem examination. He concludes that salvarsan as an aetiological factor is insufficiently proved.

Tetrachlor-ethane in the aeroplane industry and trinitrotoluene in munition work appear to have been responsible for several cases of liver atrophy during the war period. The changes have been described by Willcox (32), Spillsbury (24), Turnbull (27), and Stewart (25). The last-named observer notes the essential similarity of the lesions in 'idiopathic' atrophy and in T.N.T. poisoning, but states that the T.N.T. cases are more often of subacute type, showing *post mortem* marked red and yellow areas. The more prolonged show more or less evidence of regenerative hyperplasia.

Fraser (7) (1916), in a subacute case, referred to the liver condition as being exactly similar to that produced in a series of rabbits by diphtheria toxin, and suggested that the change was primarily due to the necrotic effect of some toxin on the terminal hepatic veins.

Jennicke (10), in 1919, reported a case of acute yellow atrophy associated with empyema of the gall-bladder and suppurative cholangitis of the larger ducts. An organism of the haemorrhagic septicaemia group grew in the primary cultures from the bile.

Huber and Kausch (8), in January 1920, reported a case in a female, aged 26, where a laparotomy for jaundice and ascites revealed a nodular subacute liver atrophy (portion removed and microscoped). A month previous sudden vomiting, diarrhoea, and jaundice had followed the eating of 'ölsardinen'. They drew attention to the large number of cases prevailing, and quoted Franz Müller as reporting 21 severe cases in one hospital during a period of six months. They referred to the numerous eosinophils found in some subacute livers: they found this in two cases; and they instanced a case of Umber's in which this was a feature.

Umber (28), writing in February 1920, drew attention to the increasing frequency of cases of acute and subacute liver atrophy in recent times. He had met with four cases in the previous five weeks and seven in 1919 in Berlin. Umber considers that syphilis plays an important part, but at the same time out of ten cases cited nine were certainly not syphilitic. He therefore argues that syphilis cannot account for the present increase, and ascribes it to the bad hygienic conditions amongst the lower classes, especially to gastro-intestinal catarrh. He lays stress on enterocholangitis as a cause and points to two cases in particular in support of this view.

Verse (29) has, also quite recently, described a case in which there was associated acute interstitial pancreatitis.

No doubt in the past many prolonged cases of subacute yellow atrophy with marked nodular hyperplasia occurring in children and adolescents have been regarded as ordinary portal cirrhoses. Rolleston (23) refers to this possi-

bility, as do also M'Donald and Milne (16), and Fraser (7) has more recently re-emphasized it. Of the occurrence of portal cirrhosis in young persons exactly similar to that in alcoholic adults there can be no question. Some of the 'family cirrheses' in children appear to be of this variety. Byrom Bramwell (4) in 1916 described a remarkable series of cases of this kind in young people: all the livers were typical examples of hobnail cirrhosis, the course was fairly rapid, and alcohol was not a factor. Bramwell suggested that these might be a phase of Wilson's disease (11) in which the nervous manifestations had not declared themselves.

The cirrhosis which is always associated with progressive lenticular degeneration (Wilson's disease) is of the ordinary hobnail type. Sections kindly shown us by Dr. Kinnier Wilson demonstrate this beyond doubt. On the other hand, Dr. Stuart M'Donald informs us that he has met with instances of more than one case of nodular subacute yellow atrophy in the same family.

The material which forms the basis of this paper consists of a series of sixteen cases of liver atrophy. They have occurred partly in our own experience (two of the cases occurred in India); they are mostly cases which have been under treatment at the Edinburgh Royal Infirmary and Sick Children's Hospital, and which have been incorporated in the teaching material of the Pathological Department of Edinburgh University. We have pleasure in acknowledging our indebtedness to Lieut.-Col. P. H. Falkner, R.A.M.C., for allowing use of the clinical notes of the two military cases, to Professor Lorrain Smith, and to several members of the medical staff of the Edinburgh hospitals for permission to utilize the other cases.

The cases fall into three groups according to the degree of acuteness of the liver change. This has been taken advantage of for purposes of abbreviated description, and in the following detail of cases the general appearances of the liver in each group have been described, followed by the particulars—clinical and pathological—of each individual case, together with remarks.

Cases I and II (Acute).

The liver was small, shrunken, with wrinkled capsule, and yellow or mottled yellow-brown in colour. Sometimes some of the darker areas would approach a deep crimson tint. The appearances might be uniform throughout the organ and the mottling appeared to be due to haemorrhagic areas under the capsule, the background being yellow or light brown.

Microscopically the liver cells had to a large extent entirely disappeared (Plate 5, Fig. 4). Isolated groups and columns were here and there observable, and in these degenerative and fatty changes were seen. These cells were granular and vacuolated with faintly staining nuclei.

The rest of the lobule appeared to consist of a shrunken fibrous reticulum in which could be seen phagocytic endothelial cells containing fat globules, and also large spaces filled with blood or altered blood. Masses of bile pigment were to be found, possibly the remains of liver cells which had undergone complete degeneration. There was usually well-marked small round-celled infiltration of

the portal tracts, but no evidence of any newly-formed bile-duct-like structures either within the lobule or extending from the portal tracts.

The other organs showed no very constant characteristic changes: there was usually marked cloudy swelling of heart muscle and of the kidney, and there might or might not be intestinal catarrh or haemorrhages into the various organs and tissues.

Case I. Pte. S. W., aged 23. Sex M. *Previous illnesses:* no history. *Present illness:* case occurred in India during epidemic of mild jaundice. From a few cases paratyphoid germs were isolated. Rapid onset of a profound toxæmia. Duration of acute symptoms, 3-4 days. *Duration of jaundice:* at least one week. *Complications:* dysentery, probably amoebic (characteristic ulcers in large bowel); calcified tuberculous glands in mesentery.

Remarks. A very acute fulminant case. The jaundice was present for several days previously, but its duration was not ascertainable. The appearances in the liver were entirely those of degeneration and necrosis, with no reaction beyond a small round-cell infiltration of the portal tracts. Fatty change was not positively demonstrated owing to want of suitable preparations, though the marked vacuolation of the liver cells would suggest its existence.

Case II. Roy. Infirmary, Edin.; Dr. H. Rainy. V. W., aged 23. Sex M. *Previous illnesses:* in hospital two months previously with syphilis. Course of treatment with five injections of salvarsan preparations. *Present illness:* admitted acutely ill as case of nephritis. Lived 36 hours; chief symptoms, delirium, coma, and haematemesis. *Duration of jaundice:* at least three days. *Complications:* none.

Remarks. A case of syphilis in which the liver atrophy followed the intra-venous administration of an arsenical compound. Almost complete disappearance of liver cells, the remainder showing a fair amount of fatty change. Little evidence of reaction except in an infiltration of the portal tracts with small round cells. Bile-duct proliferation notably absent.

Case III (Intermediate).

This was an intermediate type, and the description of the liver is as follows: Weighed 48 oz. Diminution in size not notable. Capsule very slightly wrinkled. Surface showed a very fine mottling, tiny greyish-yellow areas alternating with dark crimson-coloured ones. This appearance was uniform externally. On section the organ was tolerably firm all over, presenting again a universal finely mottled appearance—deep dark-red areas, mostly the size of a large pin-head, apparently surrounded by narrow zones of a pale brownish colour—throughout the organ.

Microscopically, the columnar arrangement was lost altogether, the cellular trabeculae having been broken up into individual cell elements (Plate 6, Fig. 5). These were much reduced in size, rounded in shape, granular, and showed vacuolation. Many were filled with yellow pigment granules. Occasional mitosis was visible in the nuclei of altered liver cells. The endothelial cells were in many cases swollen, sometimes multinucleated, and frequently contained red blood corpuscles. Though the outline of the sinusoids was not easily made out, they appeared to be dilated. There was a fair sprinkling of small mononuclear cells and a number of eosinophils present, chiefly in the portal tracts. A number of long sinuous bile-duct structures were seen in the near vicinity of the portal tracts, suggesting early new bile-duct formation. They projected somewhat beyond the portal tracts, which showed a well-marked cellular infiltration.

Case III. Pte. R. H., aged 33. Sex M. *Previous illnesses:* malaria (benign tertian). *Present illness:* commenced with apparent attack of malaria while in

hospital with venereal sore. *Duration of jaundice*: more than three days. *Complications*: syphilis (Wassermann positive); malaria parasites in blood; calcified mesenteric glands.

Remarks. This case was one preceded by syphilis and malaria and complicated by old mesenteric gland tubercle. It showed the appearance of red atrophy in which the liver cells had not completely disappeared. There was early new bile-duct formation and small round-celled infiltration of the portal tracts.

Cases IV, V, and VI.

The liver was again small and shrivelled with wrinkled capsule. The colour, however, was not uniform, there being usually a mixture of red or brown and yellow or green areas. On section the appearance varied a good deal. There might be a fine mottling due to dark crimson pin-head areas surrounded by zones of a paler and light brownish tinge; or large areas might be yellow (or bile-stained) and the rest reddish-brown or crimson (Plate 4, Fig. 1). Lobular structure was not usually to be made out, but in the deeper crimson-coloured areas the fibrous tissue reticulum could be exceptionally well seen. In consistence the organ was usually moderately soft. The distribution of the differently coloured areas in relation to Glisson's capsule was not constant, though in some cases it appeared significant.

Microscopically, for purposes of description the liver can be divided into 'red' and 'yellow' areas. The changes in the yellow areas were mainly degenerative (Plate 6, Fig. 6). The liver cells were preserved in part. They were swollen, granular, and contained numerous fat globules of varying size, as shown by sections stained in Sudan III. The fat was not confined to any particular part of the lobule. All degrees of chromatolysis up to complete disappearance of nuclei were seen.

The endothelial cells were swollen and many showed bile pigmentation. Lymphocyte-like cells appeared sparsely throughout the lobule, but in masses in the portal areas. Occasional small haemorrhages were met with, the blood escaping into the spaces left by the degenerated liver cells. Even in the most necrotic areas evidence of proliferation on the part of the bile-ducts was to be seen in the vicinity of the portal tracts.

In the red areas the changes were chiefly haemorrhagic and proliferative (Plate 6, Fig. 8, and Plate 7, Fig. 9).

The main features were:

1. Apparently complete disappearance of liver cells.
2. Haemorrhage into the shrunken reticulum of the lobule.
3. Formation of a young cellular connective tissue spreading from the portal tract.
4. Proliferation of small bile canaliculi (Plate 7, Figs. 10 and 11) and junction of these with regenerating liver cells.

Though over large areas the liver cells might seem at first sight to have entirely disappeared, careful examination would show isolated remnants of them scattered amongst the debris of the stroma and lying amongst red blood corpuscles. Probably from these cells the regenerative processes characteristic of the more prolonged cases commenced.

The appearance of areas of haemorrhage (Plate 6, Fig. 7) seemed in the first instance to result from passive dilatation of capillaries following on disappearance of parenchymatous cells; no doubt there was also an escape of red cells into stroma spaces.

Other organs might show no notable changes, or inflammatory and haemorrhagic conditions might complicate.

Case IV. Roy. Infirmary, Edin.; Dr. H. Rainy. M. G., aged 21. Sex F. *Previous illnesses*: no history. *Present illness*: admitted comatose three days before death; deep jaundice. *Duration of jaundice*: unknown, stated to be six weeks. *Complications*: old adhesive apical pleurisy; gall-stones; haemorrhages.

Remarks. This was a case of mixed 'yellow' and 'red' atrophy. There was complete destruction of liver cells in parts, many of the remaining cells showing fatty change. Bile-duct proliferation, especially in 'red' areas, was very evident. Early fibrosis was seen spreading from the portal tracts.

Case V. Roy. Infirmary, Edin.; Professor Russell. H. H., aged 38. Sex M. *Previous illnesses*: typhoid, age 9; intermittent pain left side of abdomen for three years. *Present illness*: commenced with attack of influenza (1918, autumn epidemic) eleven days before death. Comatose two days before death. *Duration of jaundice*: five days before death. *Complications*: influenzal broncho-pneumonia; phlegmonous enteritis.

Remarks. This was a case of subacute atrophy with large areas of degenerated pre-existing bile-stained liver tissue. No naked-eye nodules of regeneration were seen, but indications of regenerative activity in the liver cells which had survived. Bile-duct formation was not so marked as one would expect, but it was very evident, and there was some linking up. There was pigment from altered blood and some early fibrosis. The case was complicated by acute infective foci in the wall of the large bowel, and some broncho-pneumonia, the organs otherwise showing only toxic change.

Case VI. Roy. Infirmary, Edin.; Dr. H. Rainy. D. S., aged 12. Sex F. *Previous illnesses*: the mother's three preceding pregnancies resulted in abortions. Measles, age 5 years. Excision of tuberculous cervical gland, age 6 years. Slight influenza, June 1918. *Present illness*: ill for three to four weeks with urticaria and eczema. Symptoms were jaundice, pyrexia, and later coma. *Duration of jaundice*: seven days before death. *Complications*: none.

Remarks. This case was an early subacute one with a history of about three weeks' duration. There was relatively little disappearance of liver parenchyma; the red and yellow areas were mixed up together all through. Quite a well-marked attempt at regeneration on the part of the bile-ducts was evident, but new nodules of liver tissue were conspicuous by their absence, although there were indications of regenerative activity on the part of the liver cells.

Cases VII-XVI.

Liver was usually reduced in size, sometimes extremely so, and was firm in consistence. Occasionally a subacute perihepatitis was present. The surface was usually uneven from the projection of nodules, but in the earlier cases it would be fairly smooth or had a finely wrinkled appearance. In size the nodules varied from that of a pea to a bantam's egg, and in such latter instances oval tumour-like masses might stand out strikingly from the surface of the organ (Plate 4, Figs. 1 and 2, and Plate 5, Fig. 3). On section, the tissue as a rule was studded with nodules of newly-formed liver parenchyma, yellow in colour or yellowish-white or bile-stained. They were often seen to occur in groups, sometimes clustered in close proximity to the larger portal spaces (Plate 8, Fig. 14). The intervening tissue was mostly pinkish-grey and fibrosed in character, with intervening vascular points; sometimes it was softer, congested, and reddish-brown in colour. Ordinary lobular arrangement was absent as a rule. There was often no normal liver tissue apparent to the naked eye—the whole organ might be occupied by regenerated nodules in close contiguity to one another with little intervening stroma, or, as is usual, new liver-cell areas might be studded at intervals in a groundwork of connective tissue of varying character.

Microscopically the nodules were composed of cells resembling those of liver

parenchyma, without, however, any lobular arrangements. The cells were many of them larger than ordinary liver cells, might show mitotic changes, or might be multinucleated.

They might be much altered from terminal toxic changes, showing granular swelling, fatty globules, and nuclear degenerative changes. The nodules often contained large veins irregularly disposed and the sinusoids might be dilated. Miliary abscesses or tubercle follicles could be seen in the regenerated tissue, where there were corresponding complicating infections. The cells might be atrophied and narrowed through the mutual pressure of contiguous nodules, and similarly at the periphery of some nodules where they formed contact with fibrous tissue.

The grey tissue between the nodules was connective tissue of varying age. In its youngest form it might be vascular (Plate 8, Fig. 13). Frequently it was rich in inflammatory cells; these were largely lymphocyte-like, but endothelial cells, plasma cells, and polymorphs would also infiltrate it. Haemorrhages could be seen. Its most striking feature, however, was the presence of numerous small bile-ducts which were especially marked at the lines of junction between the nodules and the surrounding tissue.

A direct junction of those new canaliculi with the new parenchymatous cells of the nodules could often be observed (Fig. 15). Apart from nodules, liver cells could in some instances be seen in a cellular stroma, together with proliferative bile-ducts with which they were apparently forming connexion.

Vascular and haemorrhagic areas in the stroma appeared in some instances to represent the sites of the original liver lobules, the hepatic cells having disappeared and dilated blood-channels taken their places; groups of bile canaliculi were disposed as a rule peripherally to those vascular areas as if in the situation of portal tracts (Fig. 16).

Changes in other bodily organs apart from the spleen were not usually noteworthy unless there had been intercurrent disease. The spleen was usually enlarged: it might be soft or hard, corresponding with congestion and haemorrhage on the one hand or with fibrosis on the other.

Case VII. D. B. 75. Dept. Path. Univ. Edin. P. T., aged 24/12. Sex M. *Previous illnesses:* none. *Present illness:* commenced with jaundice and vomiting, later drowsiness and purpuric eruption, haematemesis and death a fortnight after onset. *Duration of jaundice:* fourteen days before death. *Complications:* fibrotic changes in kidney and spleen.

Remarks. The appearances in the internal organs indicated that pathological processes had been going on for a very much longer time than fourteen days. Liver, spleen, and kidney all showed evidence of fibrous tissue formation, the appearance of which indicated a process dating back months, possibly years. The pre-existing liver parenchyma had disappeared almost entirely. It had been replaced by fibrous tissue which was well formed; bile-duct-like structures were numerous and were seen within the liver lobules. There was a fair amount of regenerated liver tissue somewhat diffusely distributed throughout the organ, but there was at least one adenomatous nodule the size of a hazel-nut.

There might have been two distinct attacks on this liver—evidence of the first, the old fibrous tissue surrounding the bile-ducts and vessels and present in spleen and kidney: the second corresponding to the development of newer fibrous tissue.

Case VIII. Roy. Infirmary, Edin.; Professor Gulland. L. S., aged 10. Sex F. *Previous illnesses:* 'fits' since one year old. *Present illness:* enlarged spleen for eighteen months. Sore throat, &c. Terminal acute bronchitis. *Duration of jaundice:* jaundice appeared three months before death, varied from time to time. *Complications:* active tubercle of mesenteric glands.

Remarks. Case of multiple nodular hyperplasia with some intralobular fibrous tissue development and encroachment of this on parenchyma.

Bile-ducts numerous: proliferated from pre-existing and appearing at places in positions relative to lobules which suggested reversionary formation.

Case IX. Roy. Infirmary, Edin.; Sir R. W. Philip. I. C., aged 23. Sex F. *Previous illnesses:* no history obtainable. *Present illness:* started with pain and swelling in knees two months before death. Jaundice present from commencement. Improvement for a time. Eleven days before death pain in right side, vomiting, eventually delirium. *Duration of jaundice:* two months. *Complication:* foci of suppuration in liver.

Remarks. The changes in the liver were those of an atrophy of the liver parenchyma with a moderate amount of regeneration of liver tissue. The nodules were small and were scattered in clusters through the liver substance. Bile-duct canaliculi were numerous, and haemorrhage and congestion marked in the red areas.

In the small scattered abscesses we had evidence of a terminal infective process of an acute type.

The changes in the other organs were compatible with a subacute infective process of some duration with a terminal more acute one superadded.

Case X. Roy. Infirmary, Edin.; Dr. Chalmers Watson. M. S., aged 42. Sex F. *Previous illnesses:* measles in childhood. Cough and dyspnoea, 3 years. Swelling of legs and feet several years before death. Attacks of diarrhoea and vomiting with 'sickly yellow look'. *Present illness:* symptoms of influenza developed six days before death. Death from influenzal pneumonia. *Duration of jaundice:* no information. *Complications:* influenza; caseous tubercle of mesenteric glands and tuberculous nodules in liver.

Remarks. The appearances in this case indicated some previous toxic condition from which (of the organs investigated) the liver had suffered most. This was indicated by an almost entire absence of normal liver lobules, the liver cells being practically entirely of new formation. There was little evidence of the fibrous tissue, which at one time probably existed in large amount. Tuberculosis was obviously an element in the case, as indicated by the condition of the mesenteric lymph glands and a small number of metastatic nodules in the liver. Spleen and kidney also bore evidence of old damage, but showed no indication of tuberculosis.

The pneumonic condition of the lung was evidently a terminal one, due to a recent infection of the air-passages in an individual whose resistance had been lowered by imperfectly functioning liver, spleen, and kidneys.

Completeness of regeneration as contrasted with others was notable. It seemed to be a case in which, following atrophy, regeneration of the liver was fairly complete, fibrous tissue disappearing before the advancing nodular hyperplasia.

Case XI. Roy. Hosp. Sick Children, Edin.; Dr. J. S. Fowler. S. W., aged 11. Sex F. *Previous illnesses:* whooping-cough as a child. Occasional epistaxes. Never robust. *Present illness:* repeated attacks of jaundice accompanied by bleeding from gums during last seven months. Enlarged spleen. Scarlet fever a week before death. Haematemesis. *Duration of jaundice:* at intervals for seven months. *Complications:* scarlet fever. Caseous mesenteric gland.

Remarks. The history suggested that during the last seven months of life the liver was subjected to a series of repeated attacks of subacute intensity, associated clinically with jaundice and haemorrhages. Scarlet fever complicated the final attack and was an important factor determining death. The liver was a well-marked example of multiple nodular hyperplasia with well-defined yellowish areas, uniform in size, small, and tending to be arranged in clusters. The fibrous tissue was considerable in amount, grey in colour, and microscopically very cellular and containing very numerous bile-duct canaliculi.

Case XII. Roy. Infirmary, Edin.; Dr. Byrom Bramwell. L. G., aged 13. Sex F. *Previous illnesses:* scarlet fever, 5 years. Whooping-cough, 9 years. *Present illness:* enlarged spleen. Ascites, necessitating repeated paracenteses over several months. Terminal peritonitis and empyema. *Jaundice:* absent. *Complications:* ascites; peritonitis; pleurisy; enlarged spleen.

Remarks. This case was one in which the regeneration was fairly complete. Although small, the liver consisted almost entirely of parenchyma with narrow bands of fibrous tissue between the nodules. The absence of jaundice emphasized the completeness of the restitution of functional activity. There was nothing special to note about the histological appearances. The connective tissue was much looser than in ordinary cirrhosis and more cellular, and there was the usual striking bile-duct proliferation. The main disadvantage under which the patient suffered was obstruction to the portal circulation, as evidenced by enlargement of the spleen and ascites. The case terminated, as frequently happens, with acute peritonitis.

Case XIII. Roy. Infirmary, Edin.; Dr. H. Rainy. E. C., aged 10. Sex F. *Previous illnesses:* measles at 4 years. Scarlet fever at 7 years. *Present illness:* slight attack of jaundice a few months after scarlet fever lasting one month. Never regained former health and colour. Repeated bleedings from gums. Last illness began four months before death, with jaundice, enlarged liver and spleen. It was terminated by broncho-pneumonia. *Duration of jaundice:* repeated attacks. *Complications:* rheumatic fever; pyaemia; broncho-pneumonia; pericarditis and peritonitis; enteritis; caseous mesenteric glands.

Remarks. A degenerative process starting probably three years previously and possibly during an attack of scarlet fever. Subsequent to this the patient was never well and was always more or less jaundiced. The liver showed a very marked condition of multiple nodular hyperplasia with many large adenoma-like nodules, complicated by rheumatic fever and terminated by a series of acute inflammations.

Case XIV. Roy. Infirmary, Edin.; Professor Alexis Thomson. M. McL., aged 16. Sex F. *Previous illnesses:* no history. *Present illness:* admitted to surgical hospital as 'acute abdomen' with a history of two days' illness. Chest condition precluded operation. Died the following day after much haematemesis. *Jaundice:* not present at death and history unobtainable. *Complications:* acute lobar pneumonia; acute fibrinous peritonitis; tuberculosis of right kidney.

Remarks. A case of multiple nodular hyperplasia in which the liver-cell masses formed large tumour-like growths projecting from the peritoneal surface. Some of the smaller nodules tended to have a staphyloid arrangement.

Renal tuberculosis complicated the liver condition, and the immediate cause of death was acute pneumonia and peritonitis.

Case XV. Professor Harvey Littlejohn. Case D. B. 63, aged 14. Sex F. *Previous illnesses:* chorea, 12 years. Second attack chorea, 13½ years. Healthy previously. *Present illness:* admitted to hospital, October 16, 1912, with chorea. Spleen slightly enlarged. Emaciated. Was improving. On October 31 became restless, and after some sudden haematemesis died. *Duration of jaundice:* no note. *Complications:* enlarged spleen; varicose and ruptured veins at lower end of oesophagus; haemorrhagic points in stomach and bowel.

Remarks. The regeneration in this case was fairly complete, some of the nodules being very large. Fibrous tissue was well formed. There was no note of jaundice and the terminal symptoms were referable to obstruction of portal circulation. The case illustrated well the merging of bile canaliculi into liver-cell columns.

Case XVI. Chalmers Hospital, Edin.; Dr. J. S. Fowler. V. J., aged 21. Sex F. *Previous illnesses:* fairly healthy up to 17 years of age. Measles childhood. Appendicitis and tuberculous mesenteric glands operation, age 17. Never thoroughly well after. No evidence suggesting syphilis. Family history satisfactory. *Present illness:* abdominal pain, ascites, jaundice, general weakness commencing two months before death. Admitted to hospital a fortnight before death, and abdomen requiring tapping on several occasions. Towards the end became very lethargic, eventually deeply comatose. Jaundice was absent for about a week before death. *Duration of jaundice:* two months. *Complications:* acute peritonitis; acute bronchitis; gastro-intestinal catarrh.

Remarks. A large part of the liver was in a condition of nodular hyperplasia, the remainder in a state of red atrophy. The case was evidently of only about eight weeks' duration, and, jaundice having disappeared, the regenerated liver was presumably able to function satisfactorily eventually. Portal circulation being obstructed, however, she suffered from oedema and ascites. A complicating acute peritonitis was the immediate cause of death.

The Morbid Anatomical Relationships.

These cases form a fairly complete series illustrating, as we think, the various stages of a disease which represents a well-defined morbid anatomical entity, though it apparently has no constant aetiological factor. Gradations between the stages are met with, but it would appear that three types of the disease are distinguishable, each having more or less characteristic features clinically and pathologically. These are as follows:

1. *The acute type* characterized by practically universal destruction of liver parenchyma, with the minimum of reaction, and clinically fulminant, having a duration of only a few days. This is the old 'acute yellow atrophy'. The liver is small, shrunken, and yellow or yellowish-brown in colour. Of this type we have two cases, Nos. I and II. Case III is intermediate between this and the next type.

2. *The subacute type* in which in addition to destructive change there is well-marked vascular and inflammatory cell reaction, proliferation of the smaller bile channels, and early fibrosis. Clinically, as regards duration, a matter of a week or two as a rule and perhaps recoverable from sometimes. The liver in this type is still small and shrivelled, but is red or reddish-brown in colour; inasmuch, however, as there are usually patches of the more acute change left, the organ gives a parti-coloured appearance, this being a mixture of red or brown and yellow or green areas. Cases IV, V, and VI in our series are of this variety.

3. '*Multiple nodular hyperplasia.*' The type in which regeneration is the predominant feature, the organ showing adenomatous nodules of new liver tissue and being small or large according to the degree and extent of the regenerative activity. Clinically, the features are somewhat varying and the course may be very prolonged, possibly lasting for months or years. Cases VII to XVI in the series are instances of this third variety. Between the long-standing advanced examples of this type and the common so-called alcoholic cirrhosis of the liver it is difficult in some instances to draw a hard and fast line of demarcation, either

from the point of view of pathogenesis or of the final clinical picture. As the age incidence is different, and most likely the causation, we have in describing the present series of cases used a separate term in referring to those in this third category.

We suggest that for this type the term 'multiple nodular hyperplasia' be generally adopted. 'Nodular hyperplasia' is a term that has been applied for a long time to localized areas of regeneration of a liver associated with various conditions. Johannes Orth (22), in his *Pathological Anatomy* (1876), recognizes such a condition and speaks of nodular partial hypertrophies. Barbacci (1) (1901) deals exhaustively with the relationship of this condition to liver adenomata and suggests that many nodular hyperplasias following atrophy may have been classified formerly as adenomata. He rejects the view that the nodules are neoplastic and adopts the term 'multiple nodular hyperplasia', which appears to us first of all to have been used by Marchand (18) in 1895, although he seems to refer to it as a term already in use. More recently the term has appeared in German and Japanese literature, and has been used in this country by Muir (21) and Miller (20). Rolleston (23), it must be noted, points out that the relationship of nodular hyperplasia to acute liver atrophy was probably first recognized by Cayley in 1883. The introduction of an additional term carries with it always the inevitable objection, but this term is already in use and is descriptive of a fairly well defined morbid entity. The time-honoured term 'cirrhosis' has led to confusion rather than simplification. The tendency erroneously to classify nodular hyperplasias in young people following initial widespread destruction simply as common unqualified cirrhoses, has already been touched on. It constitutes a justification for urging the general adoption of a distinctive term to denote a separate clinical and pathological entity. At the same time the great difficulty in differentiating certain of the most advanced cases of this multiple nodular hyperplasia from those of 'alcoholic' 'atrophic' cirrhosis must be conceded. In the former, however, the nodules are larger, have a smooth surface, are often comparatively isolated and discrete, and frequently they are strikingly projecting and tumour-like. The intervening fibrous tissue is more vascular, softer in consistence, and varies in its amount in different parts of the liver according to the mode of regeneration. The initial atrophic process is certainly more widespread and rapid than in common 'hobnail cirrhosis', where, in all probability, small necroses produced at frequent intervals over a long period of time explain the ultimate appearances. And though the eventual clinical features of 'multiple nodular hyperplasia' are those of an ordinary portal cirrhosis in some cases, they are not so in all. It is also most likely true that the early clinical aspects differ markedly from those of common atrophic cirrhosis.

The term 'subacute liver atrophy' (or 'subacute yellow atrophy of the liver') has hitherto been universally employed in this country to denote those more prolonged cases which we have placed in this third group. As between this term and that which we suggest, it appears to us obvious that 'subacute' may be more appropriately applied to our 'Type 2'—those examples of liver

atrophy whose most notable feature is diffuse destruction of parenchyma and whose duration is longer than that of the most acute fulminating types of only a very few days' standing. In what we would generally designate 'multiple nodular hyperplasia' the most striking phenomenon is the hyperplastic and regenerative rather than the atrophic and destructive one; and the clinical course is chronic.

Analysis and remarks as to aetiology. Analysing our series from the point of view of possible aetiological factors, we get the following:

Tuberculosis. There is post-mortem evidence or a history of tuberculosis in 10 out of the 16 cases. Of these 10 cases 5 showed active tubercle present at the autopsy, one of them being renal, the other 4 mesenteric gland infections.

Syphilis. Definite evidence was obtained in two acute cases (II and III). In two others (IV and VI) there were points in the history which suggested the possibility of syphilis. One of the syphilitic cases had had five injections of novarsenobillon.

'Enterica.' There was the possibility of a paratyphoid infection in one case (I). In another there was a history of typhoid many years previously.

Scarlet fever. In two cases (XII and XIII) a history of this was obtained, and in another case (XI) it was a terminal complication.

Other preceding conditions. In one case (XV) there had been three attacks of chorea within two years previous. Amoebic dysentery was present in one acute case (I). In every case a history of some infective disease was obtained, except in instances where for some reason or other a history could not be got. But any series of fatal cases, of whatever nature, will give histories of infective diseases in early life, and such infections can scarcely be correlated with attacks on the liver unless accompanied by evidence clearly pointing to hepatic derangement.

In summarizing such cases from the aetiological point of view one must clearly distinguish between conditions which may be causal factors and those which are complications. For instance, Cases XII and XIII had scarlatina some considerable time previous to death, and this infection might conceivably have been the initial cause of the liver atrophy. Case XI died of scarlet fever, the liver being in the condition of multiple nodular hyperplasia; the scarlet fever could obviously have had no bearing on the aetiology in that case. On the other hand, the finding of a tuberculous lesion may always have some bearing on the causation. The association of active tubercle, mostly mesenteric, in five of our series of cases seems somewhat suggestive. Dingwall Fordyce (5) recorded a subacute case where there was tuberculous ulceration of the bowel. At the same time the frequency with which tubercle, active or inactive, is found in any series of post-mortems has to be borne in mind.

It would seem as if in some cases—acute—we may have probably a single virulent poison causing almost complete and rapid destruction of liver parenchyma, whilst in others—especially some multiple nodular cases—a series of repeated attacks on the liver cells may occur. It is impossible at present to make any

definite and comprehensive generalizations as to aetiology. Two points emerge apparently always in studying any series of cases, often indeed in looking at the history of an isolated one. The first is the absence of any single constant aetiological factor; the second the frequency with which a number of options is presented. Of this latter circumstance the case published by Miller and Hayes (20) in 1909 affords a conspicuous example—scarlet fever, acute rheumatism, syphilis, influenza, active pulmonary tubercle, were all elements, the last three being operative during the six months prior to the acute fatal liver disease.

The series of cases here reported, and in fact the cases generally recorded during the last few years, appear again to demonstrate only these two salient features in connexion with aetiology. They augment the number of possible causative factors, and they fail to elucidate any immediate direct determining agent, either single or multiple, constant or varying.

As a working hypothesis, Professor Stuart McDonald (15) has urged the view that two factors are concerned, there being first of all damage to the liver by, e.g., metabolic poisons, syphilis, &c., and subsequently an acute destructive action by some special virus produced in the alimentary tract. Though not entirely comprehensive this would certainly appear to be the only generalization that can be made at the moment. It necessarily of course relegates syphilis, T.N.T., salvarsan, &c., to the position of indirectly acting causes. Whether these are so or not seems at present altogether uncertain. Many points are adduced against such agencies being the immediate causes of the liver atrophy—a common one being the infrequency with which the condition supervenes as compared with the wide prevalence of the infection or toxin in question. An argument of this kind cannot be pressed too far; for instance, Addison's disease is none the less of tubercular origin, though an extremely rare manifestation of an all too common specific infection. On the other hand, an acute liver atrophy can occur directly following ingestion of a special poison. The occurrence of it in sheep as a result of eating lupins exemplifies this. And it is by no means certain that many T.N.T. cases are not directly due to ingestion toxæmia.

Considering the frequency with which damaging influences can be traced in the previous histories of liver atrophy cases and the relationship of the organ to a potentially highly infective area—namely the bowel—the idea that some special poison or poisons arising in the intestine under certain circumstances may be the determining factor cannot be dismissed without much further investigation. The cases recently investigated by Umber (28) are especially suggestive in this regard.

On the other hand, the effect of any poison, intestinal or otherwise, may be indirect although immediate. It has to be borne in mind that the real factor may lie in the liver tissue itself. The liver may contain the elements of its destruction in its own proteolytic ferments. Depression of its activities may be caused by a variety of toxic influences, general or local, slowly or rapidly operating.

'This depression, if severe enough, can prevent the liver cells from carrying out their chief function of detoxicating the portal blood. They then undergo self-digestion by their own proteolytic ferments, and this accounts for their rapid destruction. As the result of this destruction more and more undetoxicated portal blood passes into the general circulation, carrying with it the toxins of the portal blood which normally are destroyed by the liver, along with the products of liver degeneration. It is this escape of undetoxicated portal blood that causes the final fulminating toxic symptoms of the disease, and the final sudden fatty degeneration of the heart and kidney, as well as that of the remaining liver cells' (Hunter) (9).

The special changes in the liver in cases where bacteria enter the circulation are essentially patchy and focal as in typhoid fever, pneumonia, &c., whereas in the liver atrophies they are diffuse and widespread. We are inclined to think that this suggests the action of some toxin, possibly chemical, absorbed from the alimentary tract rather than any direct effect of bacteria present in the organ in the case of the liver atrophies.

Turnbull (27) (1920), reporting on a series of eight cases of post-salvarsan atrophy, appears to favour a similar interpretation as to the nature of the damaging agent. He states (in a provisional conclusion): 'The chief lesion is a very severe destruction of the liver caused by the action, probably in the more chronic cases the intermittent action, of a toxin of great toxicity and of large dosage. . . . The lesion in the liver differs, however, from those known to be caused by infection in the greater constancy of the severity of destruction or in histological details.'

Idiosyncrasy also cannot be disregarded in view of the experiences with chemical poisons in industry and the occurrence of cases of liver disease in members of the same family.

Nature and Sequence of Liver Changes in the Early Acute Stages.

As already stated, no part of the liver lobule appears to be more affected than another by the destructive agent. All parts of the liver columns undergo an atrophic process which may result in their complete disappearance.

The exact nature of the degenerative process through which the cell passes before it is completely destroyed seems a matter of relatively small importance. Undoubtedly in many cases—and probably always—fat in a demonstrable form is set free at some stage of the disease. But frequently, however, and over large areas, the cells have simply broken down by a process which may be called *necrosis*. We do not attach the importance ascribed by Stuart M'Donald (15) and others to the mode of disappearance as a means of differentiating acute atrophies from conditions such as phosphorus and chloroform poisoning and the like. In certain cases we have been able to demonstrate fatty change in the liver cells to an extent not far short of what is seen in these chemical toxæmias; e.g. Case V showed extreme fatty change. In some cases fat is apparently taken

up by endothelial cells, in which it can be demonstrated, the liver-cell columns having meantime entirely disappeared. In cases surviving some weeks many liver cells have not been entirely destroyed and persist in an atrophied condition, possessing still, however, the power of recovery and regeneration.

In several cases we have observed a marked difference between different areas of the liver as regards the amount of destruction. In two at least the indication has been that the cells occupying the anterior and upper parts of the organ have survived in a recoverable condition, whereas those in the lower and posterior parts had, so far as could be ascertained, entirely disappeared. In certain instances sub-peritoneal liver tissue had apparently been spared (in others this was not so), suggesting the possible preservative action of the peritoneal secretion under certain circumstances—conceivably neutralization of an acid poison. H. M. Turnbull (27) has observed a somewhat similar distribution in certain T.N.T. cases. Herxheimer (7a), in his recent contribution (1921), considers that the atrophic lesion begins in the centre of the lobule, whereas in phosphorus and arsenical poisoning the initial damage is at the periphery; he considers this a point against the argument that liver atrophy cases have any aetiological relationship with arsenical compounds like salvarsan.

There appears to be a marked and striking difference in the way the bile-duct epithelium is affected as compared with the liver cells. The former shows occasionally fat droplets in the cell protoplasm, but beyond this there is practically no alteration either in large or small ducts. Umber (28) has drawn attention to the coexistence of cholangitis and gastro-intestinal catarrh, but we have seen no histological evidence of an inflammatory or catarrhal affection of the bile channels. This, we believe, negatives the view that the condition arises by the direct spread of an infective process along the bile-ducts from the gut.

Once the liver-cell columns disappear, the stroma shrinks and there is collapse of the liver lobule with approximation of the portal tracts and larger vessels. There does not appear to be anything of the nature of thrombosis such as is met with in focal necroses, but the vessels, for a time at any rate, lose their lumina and the endothelial cells swell, showing vacuolation due to fat probably absorbed in phagocytosis.

Reaction and Regeneration.

One of the first evidences of reaction is a small-celled infiltration of the portal tracts. The constituent cells are those usually met with in inflammatory processes of a chronic type. In one acute case we have observed a fair proportion of eosinophil leucocytes—an observation which has also been made by Huber and Kausch (8), and by Umber (28). The next sign of reaction is a vascularization of the collapsed liver lobule associated with what may be termed in the first instance 'haemorrhage' into the stroma generally (state of 'red atrophy'). Whether this is a return of blood into pre-existing and previously collapsed channels, or how far it is due to the rupture of newly-formed capillaries, it is

extremely difficult to say. Sometimes we have seen evidence of the latter, as in Plate 6, Fig. 7. (In this the tips of several areas of liver cells are entirely haemorrhagic; and they are in close contact with Glisson's capsule, from whose vessels new blood channels are seen to be sprouting.) That the blood later on disappears and is deposited in the form of pigment within phagocytic cells is an evidence that it has been to a great extent extravascular. Marchand (18) states that in his case the blood was in large part proved by serial sections to be contained in large thin-walled vessels with little space between. He regards these vessels as being new formations, i. e. not pre-existing ones opened up. We are of a similar opinion.

Another part of the inflammatory reaction which soon manifests itself is the formation of young connective tissue. This occurs from the portal tracts and soon leads to a sclerosis of the remains of the liver lobules.

For restitution *in toto* of the functioning parenchyma there is required a proliferation of surviving liver cells and the linking up of these with excretory channels, stroma and blood-vessels being already in existence. Regeneration of parenchymatous tissue may occur in the way indicated or it may conceivably occur from the bile-ducts as in the liver in ontogeny. There can be little doubt that the first evidences of regeneration are to be seen on the side of the bile-ducts. We have no hesitation in associating ourselves with the older view of the proliferation of the bile channels occurring from their ends which were originally in contact with liver columns. We have on the one hand the observation of mitotic figures and cell and nuclear enlargement at the extremities of the interrupted ducts, and on the other hand the obvious lengthening of these smaller channels, the longer the period elapsing since the acute stage of the disease. We do not agree with McDonald (15), McDonald and Milne (16), and others, who deny altogether this proliferative reaction, and regard the greater prominence of smaller pre-existing bile-ducts as due to disappearance of liver-cell columns with which they were originally in contact. Lindsay Milne (12) claims that, reconstructing the bile-duct system in serial sections in a case of subacute atrophy, he has demonstrated their passive rôle, but this is difficult of acceptance as he does not adduce evidence of comparative investigations in normal tissues. Herxheimer (7a) more recently states he has been able to prove by serial sections that in the areas of red atrophy the new canaliculi actually come from the older ducts and are connected with their lumen.

A question of considerable interest is whether from these small bile-ducts nodules of liver tissue develop as in embryonic liver. Conditions are undoubtedly different in the two cases: in the post-atrophic condition the granulation tissue must present a hindrance to expansive proliferation. Marchand (18), Meder (19), and Stroebe (26) took the view that regenerated liver tissue can be developed from bile-ducts. This was denied by Barbacci (1). Muir (21) agrees that such a transformation may occur, but probably not to any great extent, and he questions the efficiency of such as a means of regeneration of liver tissue. We have seen no evidence of nodular development from proliferating bile-ducts

in our series in the earlier stages. In the later stages, owing to the merging of liver columns and bile channels, it is less easy to make a positive statement. We have the definite assertion of McPhedran and MacCallum (17) that such lobular development occurs.

We are inclined to the view that in the adult liver regeneration following atrophy occurs in two segments. From the liver cells new liver columns and eventually nodules of liver tissue are produced. From the bile-ducts there occurs proliferation also, and lengthening of these channels in an attempt to seek out the new liver tissue. Bile-duct proliferation, however, does not in itself result as a rule in the formation of liver parenchyma owing to the inimical surrounding conditions.

That regeneration occurs first of all on the part of the bile-ducts is probably owing to their lower character as epithelial cells. The liver cell being more highly specialized takes longer to recover itself. During the acute stage of the disease the undestroyed liver cells are shrunken and atrophied. As the condition becomes chronic and the stimulus to regenerate (the 'formative Reiz' of Weigert) (30) affects the cells, they swell up, absorb moisture from their surroundings, and assume an appearance as depicted in Plate 7, Fig. 9. Such cells are numerous at a certain stage of the disease, and we have seen them in very large numbers in Cases V and VII in the present series. The protoplasm then becomes condensed and cell proliferation occurs mainly by direct division apparently. In none of our cases have we seen mitotic figures in liver cells as depicted by Meder (18). The transition between the enlarged vacuolated cells and those with the denser protoplasm is well seen in Plate 6, Fig. 8, and Plate 7, Fig. 9. It is from such groups of cells that new nodule formation takes its origin. These nodules show the usual microscopic appearance of normal liver tissue except that the lobular arrangement is absent.

In suitable early cases the developing nodules show a cluster-like arrangement, the groups being formed in relation to the larger portal channels and areas of Glisson's capsule, following, in other words, the same initial distribution as the process of vascularization. No doubt there is a direct connexion between this organization and the rousing of surviving liver cells into regenerative activity. In certain other cases where large areas of liver tissue are spared, regeneration on a massive scale occurs without this discrete cluster arrangement of nodules.

Probably from the commencement this new nodular liver tissue is capable of functioning as evidenced by the presence of bile coagula. But until the nodule gets into continuity with bile channels bile cannot be excreted. Thus the bile-stained character of the earlier areas of regeneration. There are, however, already immense numbers of new bile-ducts in the immediate vicinity and the linking up of these with the new parenchyma is easily understood.

Degenerative change of a fatty nature is often observed in isolated nodules, as was noted by Barbacci (1). He ascribed this to imperfect blood-supply due to insufficient junction of their capillary system with the main vessels of the organ. This may very well be the case; but where, as often, the fatty change is

more widespread it is to be put down to toxic effects from accompanying acute infections, e.g. peritonitis, enteritis, pneumonia.

Liver cells having been re-formed and having established connexion with the already proliferated bile-ducts, and there being in existence a vascular stroma connecting with the main blood channels, there seems no reason why the organ should not function. We are of opinion that the regenerated liver can carry on all the functions of the organ, though perhaps somewhat hampered. The formation of tumour-like new nodules projecting beyond the surface as in Case XIV (Plate 5, Fig. 3) seems to indicate that regenerative changes are not prevented by fibrous tissue to the extent sometimes supposed.

Associated Conditions, Complications, and Terminations.

In the liver atrophies the other organs, as a rule, show no constant characteristic change. In acute cases there is always a marked degenerative change in the kidney which may amount to a catarrhal nephritis. The relatively small effect on the kidney parenchyma as compared with the liver seems to favour the idea that the causal poison is a portal rather than a systemic one. Indeed, the renal changes might in large part be explained by the coexistence of jaundice. In the more chronic cases, such organs as kidney and heart show usually little alteration, unless some slight evidence of previous infections or cloudy swelling, &c., from terminal inflammations. The spleen in the acute cases shows the appearances simply of toxic swelling. In the more prolonged it is in most instances enlarged, the increase being slight, moderate, or very great in different cases. As regards the causation of the marked and sometimes excessive enlargement met with, we are prepared to say little except that it does not appear to be due to chronic inflammatory change in the organ and is in all probability a result of obstruction of blood-flow through the liver. The great size of the organ in some multiple nodular cases has caused difficulty in diagnosing the condition from Banti's disease during life. In the present series the spleen was enlarged in 9 out of 10 prolonged cases; in 4 cases it was greatly enlarged, in one instance weighing 480 grm.

No notable alteration was seen in the alimentary tract as a rule in the cases we have dealt with apart from haemorrhages in acute fulminant examples. This does not detract, in our opinion, from the significance of the view that the poison is intestinal in origin. In three cases out of the whole series there was an intestinal lesion, in one a healing amoebic dysentery, in a second a phlegmonous colitis, and in another an inflammatory and haemorrhagic infiltration of the lower ileum and upper half of the colon. In the first—an acute fulminant case—the bowel lesion was most likely accidentally coexistent, and probably had nothing to do with the liver change. The other two, which were prolonged cases, simply exemplify the marked susceptibility to acute inflammatory complications which in the particular instances attacked the intestine. Jaundice is always present in acute and subacute cases. In the multiple nodular stage

it may or may not be a feature, and when present may be only for intervals. Its absence in some cases emphasizes the completeness with which function can be restored.

Attention has been directed to the coexistence of cholangitis. We have not in this series of cases met with any instance of this. Case IV had gallstones, but no evidence of mechanical or inflammatory obstruction of the bile passages.

As regards the mode of death, the more acute and early cases die from a profound toxæmia associated with jaundice as a direct result of want of liver tissue. Where the duration is prolonged and nodular hyperplasia has commenced the termination may be in similar fashion, but much more usually from a superadded acute infection, commonly pneumonia, peritonitis, and such-like; sometimes influenza. In the present series, the immediate cause of death in 9 out of 10 prolonged cases was some acute inflammatory or infectious disease. The other case (No. VII) died with symptoms pointing only to hepatic insufficiency, there being no complicating septic infection.

Summary.

Liver atrophy shows three distinct types representing changes through which the liver may pass. These should be termed: (1) Acute atrophy; (2) Subacute atrophy; (3) Multiple nodular hyperplasia of the liver.

The actual cause is undetermined; and there is no histological evidence in the cases we have examined to indicate that the condition arises by the direct spread of an infective process along the bile-ducts to the gut.

Regenerative changes are manifested first in the bile-ducts, this resulting mostly in the production of ramifying canaliculi; but new liver-cell nodules arise mainly from spared liver cells which, in the first instance degenerated, later on swell up and subsequently multiply by direct division to produce new parenchyma. The liver can regenerate sufficiently thus to carry on its work for an indefinite period.

Jaundice is always present in the acute and subacute cases; in the multiple nodular hyperplastic ones it may be present or absent.

In fatal cases the other organs show no constant characteristic change. In the prolonged cases, splenic enlargement—slight, moderate, or enormous—is the rule.

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DESCRIPTION OF PLATES.

PLATE 4, FIG. 1. Case V. Naked-eye section of liver. The anterior two-thirds of the section was brownish-yellow and microscopically showed great destruction of liver cells. The posterior third was mottled, greenish areas composed of bile-stained and degenerated liver cells alternating with light brownish-yellow parts. A subacute case.

FIG. 2. Case XIII. Naked-eye section. A characteristic example of 'multiple nodular hyperplasia'. Surface uneven from the presence of projecting nodules separated by vascular depressions. The organ was studded with pale whitish-yellow and slightly bile-stained, circumscribed and well-defined nodules, especially in its upper two-thirds.

PLATE 5, FIG. 3. Case XIV. Naked-eye section. Liver was reduced in size and showed a strikingly nodular surface, some nodules projecting so as to simulate tumour masses. Substance of organ showed whitish nodules of all sizes separated by a dark vascular stroma.

FIG. 4. Case I. (Acute atrophy.) Liver. Low-power view. Showing almost complete destruction of liver parenchyma; only a few columns of liver cells still visible. Lobules collapsed. Small round-celled infiltration of portal tracts, but no other evidence of reaction. Haem. eosin.

PLATE 6, FIG. 5. Case III. (Intermediate between 'acute' and 'subacute' atrophy.) Low-power view. Extensive atrophy of liver-cell columns; vascularization of liver lobules and small-celled infiltration of portal tracts. Haem. eosin.

FIG. 6. Case IV. (Subacute atrophy.) High-power view. Necrosed and degenerated columns of liver cells seen; also extensive disappearance, with collapse of lobules, vascularization and haemorrhage; early bile-duct proliferation. Haem. eosin.

FIG. 7. Case IV. (Subacute atrophy.) Low-power view. From a 'red' area: showing areas of haemorrhage immediately subjacent to Glisson's capsule, from which new blood channels are sprouting. Haem. eosin.

FIG. 8. Case V. (Subacute atrophy.) High-power view. Degenerated and vacuolated liver cells, phagocytic endothelial cells, and small bile-ducts filled with pigment. Bile-duct proliferation and junction with liver cells. Haem. eosin.

PLATE 7, FIG. 9. Case V. (Subacute atrophy.) High-power view showing early stage of regeneration of liver from cells which, having survived the acute degenerative stage, swell up and become vacuolated; later their protoplasm becomes more dense and more deeply eosinophil. Haem. eosin.

FIG. 10. Case VI. (Subacute atrophy.) Low-power view of an area showing proliferating and branching bile channels with early regenerative change in liver cells and fibrosis. Haem. eosin.

FIG. 11. Case VI. (Subacute atrophy.) High-power view of a branching bile channel; extending towards and effecting junction with regenerating liver cells.

FIG. 12. Case VIII. (Multiple nodular hyperplasia.) Nodule of regenerating liver tissue pressing aside the surrounding fibrous tissues, in which are many small bile channels. Haem. eosin.

PLATE 8, FIG. 13. Case IX. (Multiple nodular hyperplasia.) Nodules of regenerated liver tissue lying in a cellular fibrous matrix. Numerous minute bile-ducts disposed as a rule peripherally to the vascular interstitium. Haem. eosin.

FIG. 14. Case IX. (Multiple nodular hyperplasia.) Showing tendency of the regenerating nodules to be arranged in groups in relation to the larger portal spaces.

FIG. 15. Case XI. (Multiple nodular hyperplasia.) Showing groups of bile-ducts and of regenerating liver cells, and emphasizing the similarity between the two, and the possible transition from one to the other.

FIG. 16. Case XV. (Multiple nodular hyperplasia.) Showing an area of proliferating bile-ducts and liver cells in a cellular stroma, with absence of any distinct demarcation between liver cells and bile-duct-like structures.

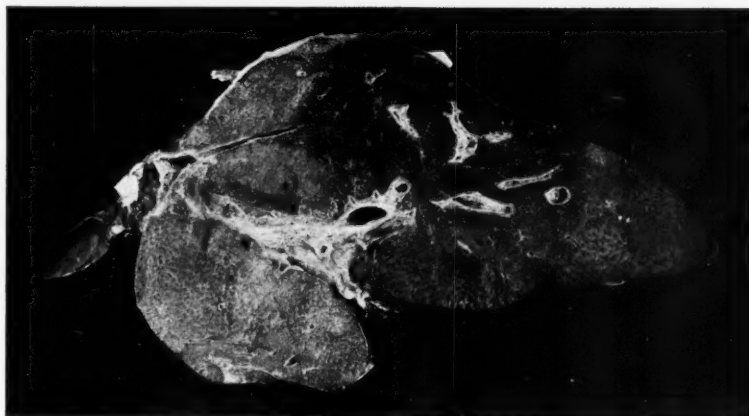


FIG. 1

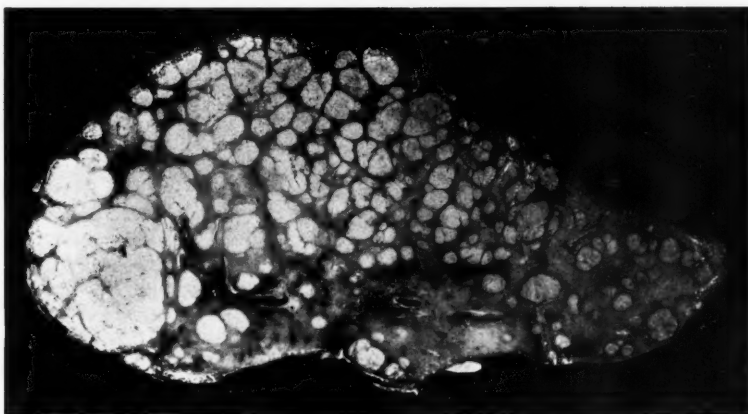


FIG. 2





FIG. 3



FIG. 4



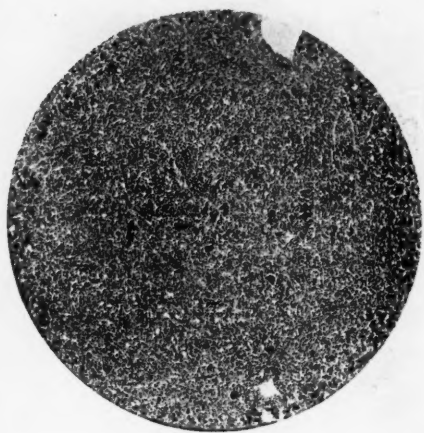


FIG. 5

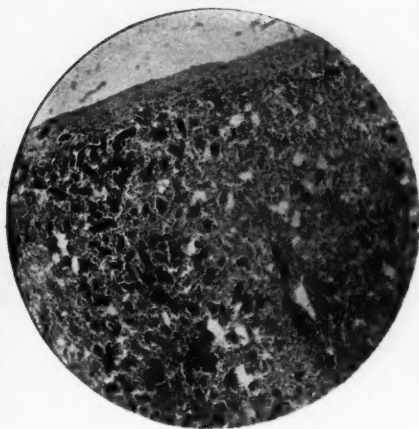


FIG. 6

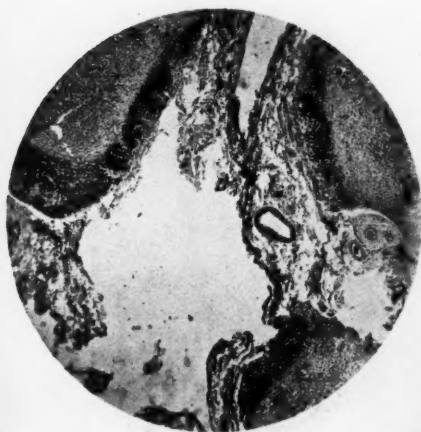


FIG. 7

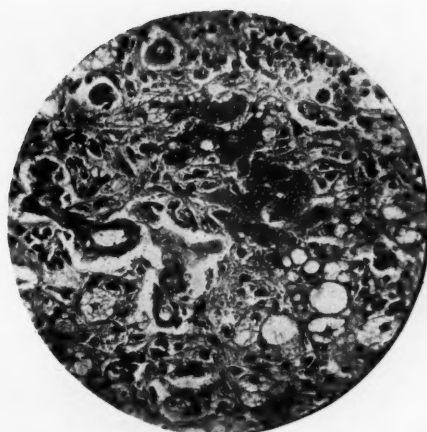


FIG. 8



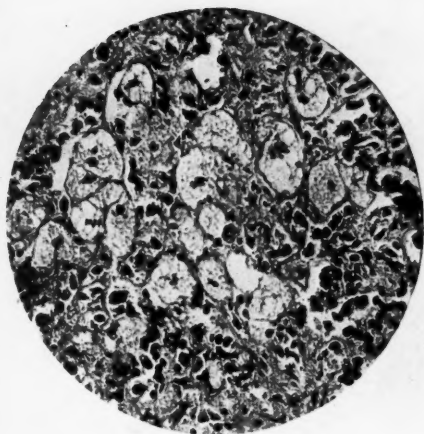


FIG. 9

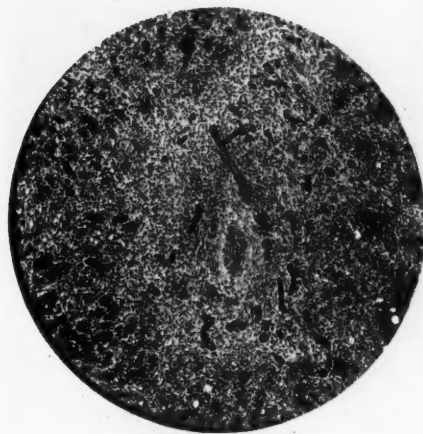


FIG. 10

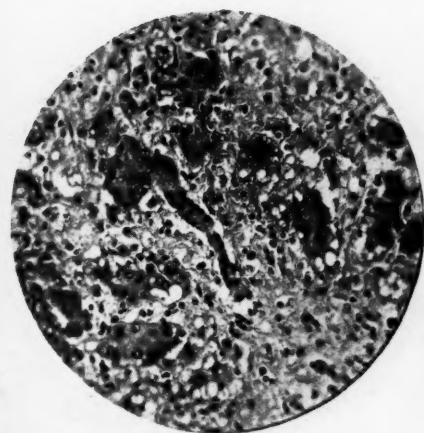


FIG. 11

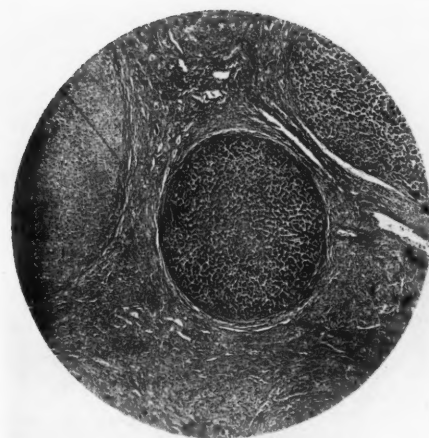


FIG. 12



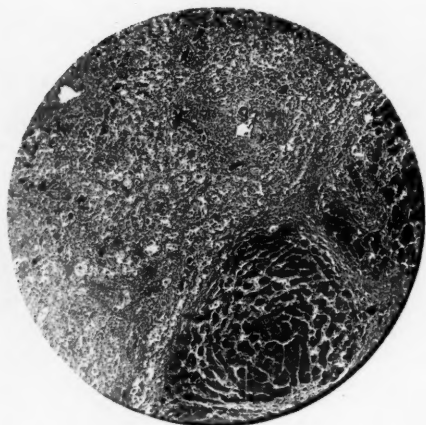


FIG. 13

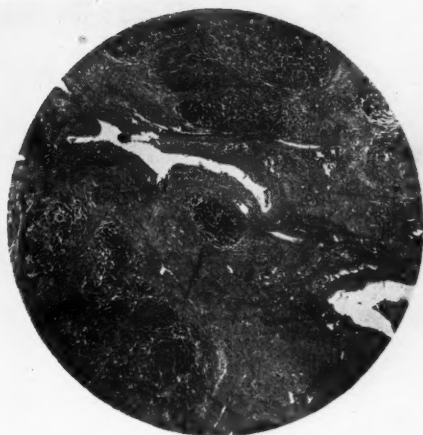


FIG. 14

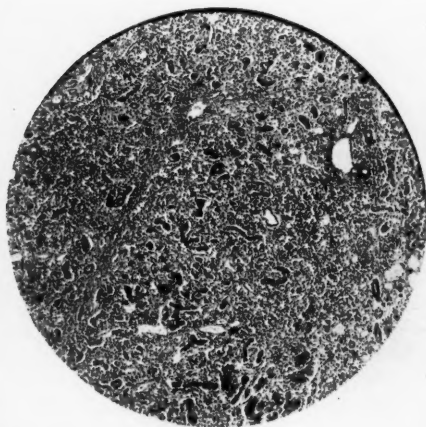


FIG. 15



FIG. 16



GENERALIZED MYOSITIS FIBROSA, WITH THE REPORT OF A CASE

By J. A. G. BURTON, JOHN COWAN, AND HUGH MILLER

(From the Glasgow Royal Infirmary)

With Plate 9

Description of Case.

The following case seems worthy of record on account of the rarity of the condition. We have only been able to collect five cases in the literature.

The patient, a married woman, aged 25, was admitted into hospital on September 13, 1920, complaining of stiffness of the arms and legs of some three months' duration. She had always enjoyed good health save for some disease of the left tibia, which required operative interference, at the age of 12. She had borne four healthy children.

In February 1920 she became pregnant for the fifth time, and shortly afterwards thought that her legs were somewhat stiff, but she was not seriously incommoded and continued to perform her household duties. In May, however, she miscarried and was curetted twice. She made a good recovery, but in June the stiffness of the legs was distinct, and she was unable to walk for any distance. Her arms, too, were now affected. In July her symptoms steadily progressed, and in the beginning of August she became so helpless that she had to take to bed. Her left shoulder was painful at times, especially at night, but she had no pain elsewhere, and her difficulty lay in the stiffness, which, she said, was in the muscles and not in the joints.

For a fortnight before admission, her face and feet were sometimes swollen during the daytime, but this disappeared during the night. She stated that she was quite well in every way apart from her helplessness.

During her pregnancies she had always been liable to sore throat, and in June an attack had rendered her unable fully to open her mouth for a few weeks.

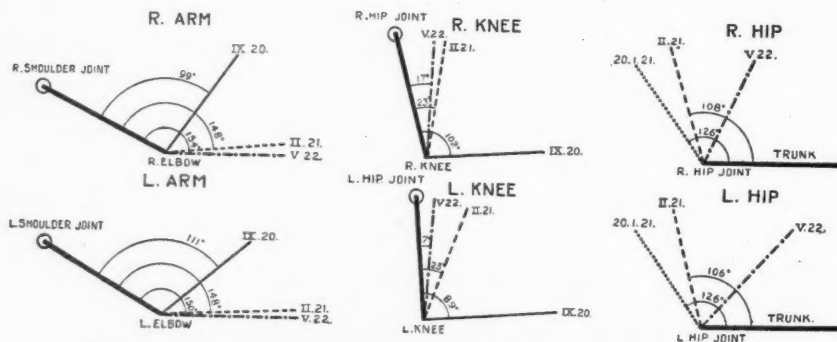
On admission, she was found to be a tall, well-built woman and fairly well nourished, though she said that she had lost flesh since the onset of her illness. She lay comfortably in bed on her back, but was quite helpless, being unable to turn on her side without assistance, while the movements of her limbs were so restricted that she was practically unable to attend to herself in any way. The back was straight, stiff, and immobile, the legs extended, and the arms partly flexed. The movements at the joints, quite free within certain limits, were suddenly stopped at definite angles from the tightness and shortness of the muscles. She was thus unable to touch her eyelids with her fingers, or to extend the arms fully. The movements of the toes seemed normal, but she was unable to flex the ankles to a right angle. Flexion of the knees was very limited, and she was only just able to raise her feet off the bed, though the lateral movements

of the hips seemed fairly free. The diaphragm was acting, but the thoracic expansion only measured 3 cm. The movement of the fingers was ample but weak. The movements of the wrists were fair, save that, while pronation was full, supination was notably defective. The extension of the elbow was limited, and the movements of the shoulder-joints very slight (see diagrams below).

The ocular and facial muscles, the masseters, the diaphragm, and the muscles of the fingers and toes alone seemed capable of full movement.

There was a fair amount of subcutaneous fat upon the limbs, which showed everywhere a rounded outline, the normal muscular contours being lost. All the muscles were definitely atrophied, and the possible movements were extremely weak.

The limbs imparted a peculiar sensation to the fingers, the muscle feeling firmer and stiffer than normal, and not unlike a sand-bag or piece of wood. The electrical reactions of the muscle affected were normal, save that the amount of current required was excessive.



Diagrams showing the degree of movement of the joints on the patient's first admission into hospital and on subsequent dates.

The joints, on general and X-ray examination, proved sound. The superficial reflexes were normal, except for the absence of the epigastric and abdominal ones, but the deep reflexes, biceps, triceps, quadriceps, and tendo Achillis were absent. There was a minimal amount of oedema in the feet. Throughout her residence the skin was always moist. Sensation was normal.

The organs seemed sound and functioned well. A swab from the uterine cervix proved sterile, but the urine, which to the naked eye and on chemical examination appeared normal, showed a gross coliform infection, a platinum loopful of the unsedimented urine yielding over 200 colonies in an ordinary agar plate. There was, however, no fever and no urinary symptoms.

To confirm the diagnosis, a small portion of the left gastrocnemius muscle was excised for microscopical examination. The exposed muscle appeared darker in colour, and felt definitely denser in consistence than normal.

Microscopically, there was a general increase in the connective tissue of the stroma, with several patches of active inflammatory reaction.

In the inflamed areas the extensive increase in the interstitial tissue was accompanied by marked degenerative changes in the muscular elements. Many of the muscle-bundles had apparently disappeared, while others showed varying degrees of atrophy. A few muscle-bundles in these patches showed hyaline and vacuolar degeneration, but these changes were more strikingly shown in isolated bundles elsewhere. In the areas of hyaline change, the muscle substance appeared granular and structureless with a tendency to polychromatic staining. (Ehrlich's triple stain with haematoxylin was used.) A limited zone of round-celled infiltration surrounded the less affected bundles, while the more degenerate

bundles had their substance and surroundings invaded by large mononuclear phagocytes. The areas of vacuolar degeneration were devoid of any reactive zone, the vacuolar spaces appearing either in the centre of the bundle or round its periphery.

Vascular changes were present in the form of a rather chronic arteritis, with a limited surrounding small-celled infiltration; these changes were general, but most marked in the inflammatory areas.

A large number of the muscle-fibres exhibited loss of transverse striation (Figs. 2, 3, 4, 5), this appearance being more obvious when the sections were examined by polarized light.

The electrical reactions were tested on September 18, 1920, with the following results:

Orbicularis oris contracted normally to the faradic current. With the galvanic current 2 ma. produced a contraction, KCC being greater than ACC. The abductor minimi digiti required 3 ma. and the interossei 4 ma.; there was but little difference between KCC and ACC. The flexors of the fingers reacted to 1.5 ma., while the flexor carpi ulnaris required 3 ma. The gastrocnemius and tibialis anticus required very strong faradic currents to produce contractions; with the galvanic current the tibialis anticus required 10 ma., KCC being greater than ACC.

The patient's progress after admission was very slow, but continuously in the right direction. In the beginning of October she was able to touch the roots of the hair upon her forehead, and the possible flexion of the legs at the knees was of greater extent than in September. In November, when sitting in a chair, she was able to raise her feet off the ground, but even a month later she was unable to place her hands behind her neck, while the movements of the spine were practically minimal. In January 1921 she began to use the go-cart, but she was quite unable to grasp the handles firmly, or lift her feet off the ground. In February, however, she began to walk fairly well, could put her hands behind her neck, and even dress her hair for herself. At the end of the month she was walking comparatively steadily with the merest support, and that rather psychical than mechanical.

In June she was performing all her domestic duties without difficulty, her movements being more free, and the only absolute defect was in dorsiflexion of the right foot. With the use of $1\frac{1}{4}$ in. heels, however, no inconvenience resulted.

She came again under observation in May 1922. Her condition was satisfactory and the possible movements of the joints more free than they had been in the previous year. The muscles, too, for the first time, had lost their 'sand-bag' feel, and they were now, though distinctly hard, not more so than is often the case in the muscles of elderly working men.

She stated that she had remained well until October 1921, when, being again pregnant, she had miscarried after an accidental fall. On recovering, she thought that the stiffness was increasing, and again sought advice. Notwithstanding her complaints, it was quite obvious that the muscular condition had improved, and a few days' residence in hospital restored her confidence.

The nature of the muscular inflammation suggested an infection as its cause, but a careful, detailed examination failed to reveal any source of sepsis beyond the infection of the urinary tract. This, as has been already mentioned, was grossly infected, though no symptoms of urinary discomfort were experienced. Under alkalis, the infection speedily lessened, and the urine was sterile in May 1921. In May 1922 the urine was still sterile.

The subsequent progress of the patient has not been as satisfactory as had been anticipated. Owing to the depression in trade, her circumstances became difficult and she was exposed to considerable privations. In August 1922 she began to experience pains in the back, the left hand, and the soles of the feet. In September she became more stiff, and unable to work while on her knees—for instance, when washing the floor. She was readmitted into hospital, for the third time, in November 1922.

On admission she was very nervous and sorry for herself, and disinclined to help herself in any way, but she soon began to recover her nerve. The movements of the larger joints were as good, or better, than they had been on her last dismissal from hospital, the muscles having lost their wooden character, and now differing but little from those met with in elderly working men. She was still unable to dorsiflex her right ankle completely, the dorsal spine was still very stiff, and the hands were now for the first time affected. The movements of the fingers were definitely restricted, and the muscles were hard and small. The overlying skin, too, was involved, and was dense, shiny, and rather blue, while some tiny ulcers were present over the proximal interphalangeal joints. Passive movements of the fingers were painful.

The urine again showed an abundant coliform infection, though urinary symptoms were absent, and the urine was apparently normal to chemical tests.

Her progress was satisfactory, and she put on weight. The blueness of the fingers disappeared, but the skin of the fingers, and to a lesser degree that of the hands, remained less mobile than elsewhere and thicker, resembling pigskin. The movements of the fingers improved considerably, but she still complained of difficulty in using them for delicate work on dismissal from hospital in February 1923.

The electrical reactions were unaltered save that the response of the intrinsic muscles of the hand was only moderate in their degree.

She was a 'soft' woman from the mental standpoint, and while she reacted quickly to the sympathetic attitude of the nursing staff, she evidently had difficulty in accommodating herself to her physical infirmities, and lost heart quickly when at home.

Discussion.

There is a good deal of confusion even yet with regard to the classification of the different inflammatory affections of the muscles. Batten's (1) classification is as follows :

A. PRIMARY AFFECTIONS OF MUSCLES.

(1) *Polymyositis*, including acute polymyositis, dermatomyositis, haemorrhagic myositis, polymyositis with erythema multiforme and urticaria, and pseudo-trichinosis.

(2) *Neuromyositis*.

(3) *Tuberculous myositis*.

(4) *Syphilitic myositis*.

(5) *Myositis due to Trichinella spiralis*.

B. SECONDARY AFFECTIONS OF MUSCLES in the course of some acute or chronic disease.

(1) *Myositis* in the course of specific fevers such as enteric, typhus, small-pox.

(2) *Infective myositis*, occurring in pyaemia, infective endocarditis, glanders, gonorrhoea, puerperal infections, infected wounds, actinomycosis, erysipelas, &c.

C. MYOSITIS WITH SPECIAL TERMINAL LESIONS.

(1) *Myositis ossificans*.

(2) *Myositis fibrosa*, either generalized or local.

Steiner (2) defines myositis fibrosa as follows: 'A single or multiple inflammation of the muscles, mostly subacute or chronic, which generally begins in the lower extremities, and presents but slight constitutional symptoms. Eventually the muscle-tissue concerned is largely or wholly replaced by connective tissue, and quite pronounced muscle atrophy may be then observed.'

Volkmann was apparently the first to point out that myositis fibrosa must be separated from other forms of acute and chronic myositis, and also from the 'rheumatic callosities' in muscle described by Floriep.

In *acute infective myositis* the onset is sudden, with pain, fever, and other systemic disturbance, and the cause can be presumed with a fair degree of certainty. The disease is limited to one group of muscles, and complete resolution occurs in a few weeks. Cases of this type, where the gonococcus was the causative organism, have been described by Treves (3), Eichhorst (4), Batut (5), and Ware (6).

In all these a recent attack of gonorrhoea had occurred. In Ware's case the affected muscle was incised and the organisms recovered. In Batut's case the infiltration was so dense that myositis ossificans was suggested as a diagnosis.

In other cases the condition has followed furunculosis. Scriba (7) describes an unusual case of this type, where the involvement was more widespread than usual. The patient, a medical student, who had previously suffered from some boils in his neck, took ill suddenly and acutely with intense pain in the left elbow and right thigh—the left thigh being involved later. The muscles were greatly thickened and felt like a 'plaster case'.

Myositis fibrosa, the Localized Form.

The diagnosis of local myositis fibrosa is difficult, for it may be even closely simulated by chronic muscular rheumatism or fibrositis, in which only the white fibrous tissues, and not the muscle proper, are involved. Thus, Bergmann (8) describes as chronic myositis the case of a man aged 66, who developed 'knotty' painful swellings of the latissimus dorsi, pectoral and serratus muscles, which were completely cured by massage. In myositis, on the other hand, the muscle itself is affected, and in a uniform manner. We have found four cases in the literature where the diagnosis was verified by examination of the muscle. They are described by Krukenberg (9), Hackenbruch (10), and Lindner (11).

In Krukenberg's case there was a previous history of rheumatism. The patient, a male, began to suffer from swelling and stiffness in the right thigh. The extensors and adductors were chiefly involved and the overlying skin felt thickened. The case was sent into hospital as an osteosarcoma for high

amputation, but Trendelenburg, from his experience of Gies's case (described later), advised excision of a portion for microscopic examination, when the diagnosis of myositis was made. The condition improved rapidly under faradization and massage, an almost complete cure resulting.

In Hackenbruch's case, a 19-year-old workman, the illness had commenced six months before with headache and giddiness, followed by pain and stiffness in the left thigh. The process had extended to the calf-muscles before admission. On admission the left knee-joint was fixed at an angle of 170° , with no active movement and 5° of passive movement. The diagnosis seemed to lie between osteomyelitis and sarcoma. An incision was made and the knee-joint punctured. The diagnosis was made microscopically. Treatment by massage and electricity resulted in a slow and incomplete recovery.

Lindner describes two similar cases in which the diagnosis was made by incision and microscopical examination. In the first, a woman of 20, the history was of gradually increasing fullness in the right iliac fossa, with some pain but no fever. After incision, when the whole muscle mass in the iliac fossa was found to be involved, a gradual and almost complete recovery took place.

The second case showed the disease in an advanced condition, and little improvement resulted. The patient, a woman of 53, had suffered for eight years from a gradually increasing swelling in her left thigh. The condition spread to the calf-muscles, and she had been bedridden for a year before admission to hospital; pain was a prominent symptom in the later stage of the disease.

The whole thigh and calf felt 'as hard as wood' on admission and the overlying skin was thickened. Multiple incisions served to dismiss sarcoma and osteomyelitis and to establish the diagnosis.

Myositis fibrosa, the Generalized Form.

This form, too, seems to be rare, and we have discovered but five cases in the literature. We do not think that the diagnosis has been missed, for the condition of the muscles is very characteristic, and in our experience has only been simulated by cases of dermatomyositis, which differ completely by the involvement of the skin. The wood-like, sand-bag feel of the muscles is very characteristic.

In the case described by Gies (12), a business man of middle age began to suffer from swelling and stiffness at the lower end of the right thigh. The muscles of the calf were involved later, and the left thigh muscles were also slightly affected. The onset was gradual, without fever. The swelling was 'board-hard' and sensitive to pressure, while the overlying skin was thick and unyielding. By exploratory incision Trendelenburg made a clinical diagnosis of myositis fibrosa, but the portion excised for microscopical examination was lost.

Treatment carried out for some months by baths, massage, and electricity resulted in a partial cure.

Gies considers that an aetiological factor in this case was a carbuncle, from

which this patient suffered some weeks before the onset of his muscular condition. The author emphasizes the rarity of the condition, and speaks of the 'wood-like' hardness of the muscle as pathognomonic.

Kreiss's (13) case occurred in a male, aged 30, who, nine years previously, had suffered for some weeks from stiffness and pain in his right leg. The condition at that time cleared up without treatment.

Nine years later he began to suffer from pain and stiffness in both calves. The disease gradually spread to both thighs and he became bedridden. There was no fever. On his admission to hospital the calf-muscles felt sinewy hard, and both feet were in the equinus position from contracture of the affected muscles. The muscles on the inner side of both thighs felt 'cord-like'.

No histological examination was made.

Treatment was carried out by salicylates, massage, and electricity. After five months in hospital the patient left greatly improved and able to walk. A year later Kreiss heard that the improvement had continued, although recovery was by no means complete.

In Janicke's (14) patient, a male aged 19, the sterno-mastoids were first involved, pectorals, serrati, and trapezii becoming affected later. The onset was gradual, with an occasional day's fever. Diagnosis was confirmed by excision of a portion of muscle.

Treatment by massage and electricity resulted in almost complete cure.

The author admits that the aetiology of the case was obscure, and his histological description of the muscle in the early and advanced state of the disease is the fullest that we have been able to discover.

Gowers's (15) patient was a woman, aged 36, who only came under his observation two years after the onset of her symptoms, which had succeeded the strain of nursing her mother throughout a long illness. At this time she was much exposed to cold at night, and was often overtired. At the outset she experienced considerable pain in the muscles, but this lessened after a time and the muscles gradually became atrophied, stiff, and extremely hard and firm, so that movements were difficult and limited, and she became practically helpless. The muscles of the neck, trunk, arms, and legs were involved, the facial muscles stiff, and the masseters contracted. The sphincters were not affected. The skin, as in our case, sweated profusely. The electrical reactions were normal, save that a large current was required. As the muscles which were least paralysed were the most contracted, Gowers considered that the nerves must also be involved. Some improvement resulted, and she was ultimately able to walk, but regained little use of her hands.

No obvious cause for the illness was apparent, and Gowers talks in a general way of a rheumatic infection, as her father had suffered from gout and rheumatism.

In Batten's (16) case, a boy aged 6, the disease commenced in infancy. The aetiology was obscure, and the patient was in a practically hopeless condition when he came under the author's observation. The muscles of legs and back were involved, the patient lying partially doubled up in bed. There was no

fever and little pain except when efforts were made to move the affected muscle. The case progressed to a fatal issue.

We regret that we are unable to offer any definite opinion as to the aetiology of the disease. The histological appearances are those of a subacute inflammation of the muscle, and not of an ischaemic degeneration, but the causal agent was not determined. The possibility of infection by an animal parasite seems excluded by the histological examination. The possibility of infection from the throat or the uterus seems negatived by the occurrence of symptoms prior to the onset of the curettage and the sore throat. The only other visceral abnormality was the urinary infection, but this was not associated with any urinary symptoms and was merely a bacteriological finding, and we are not inclined to lay much stress upon the connexion in view of the frequency of coli infections of the urine and the infrequency of myositis fibrosa.

Histological examinations and naked-eye appearances in previous records apply almost exclusively to the disease in its advanced or final stage, where fibrosis has almost obliterated the muscular elements, and the mottled appearance of the exposed muscle is characteristic. Janicke, however, gives a description of the microscopic appearances in an early case, and this corresponds closely to the histological findings in this case.

Lorenz (17), in his description of the naked-eye and microscopic appearances in this disease, appears to rely chiefly on the descriptions by Hackenbruch and Janicke, and emphasizes the loss of transverse striation, stating that this is usually accompanied by an accentuation of the longitudinal markings—an appearance which was not observed in this case.

The satisfactory result in this case, although the general measures adopted and the elimination of the urinary infection must be considered, was chiefly due to the unremitting care and patience of Miss F. G. S. Munro, masseuse to the Royal Infirmary, whose constant attention produced a result quite above what had been hoped for, and one which has only been equalled in a single recorded case.

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DESCRIPTION OF PLATE.

PLATE 9, FIG. 1. Section of normal muscle for comparison with Fig. 2 (4 mm. obj., No. 4 ocular).

FIG. 2. Section of affected muscle, the same magnification as Fig. 1, showing the general increase in the interstitial tissue with the patches of definite inflammatory reaction. The degeneration of the muscular elements is quite evident.

FIG. 3. An isolated muscle-bundle showing advanced hyaline degeneration. The muscular tissue has almost disappeared and a cluster of mononuclear phagocytes has invaded the debris (4 mm. obj., No. 4 ocular).

FIG. 4. Isolated muscle-bundles showing vacuolar degeneration (4 mm. obj., No. 4 ocular).

FIG. 5. Section of an inflamed patch in the muscle under higher magnification than Fig. 2. The degenerative changes in the fibres and arteritis are more obvious under the higher magnification.

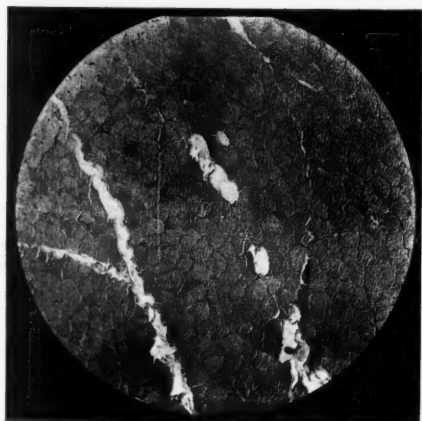


FIG. 1

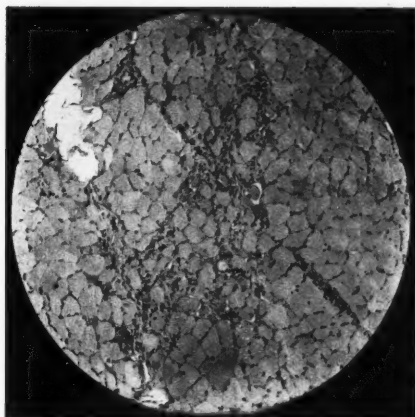


FIG. 2

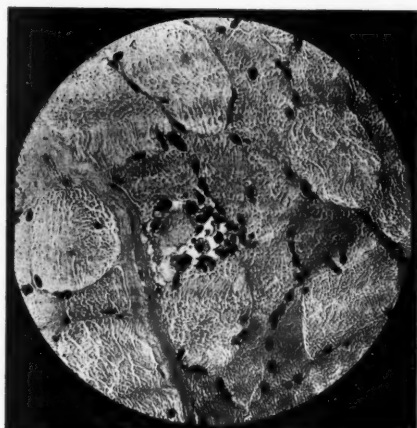


FIG. 3

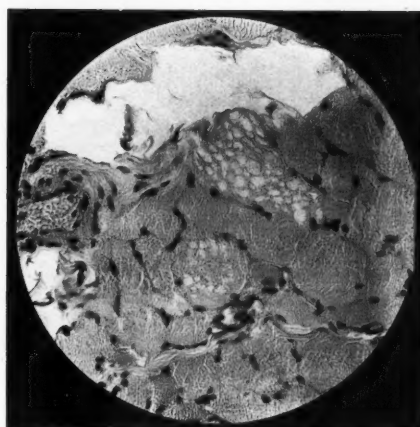


FIG. 4

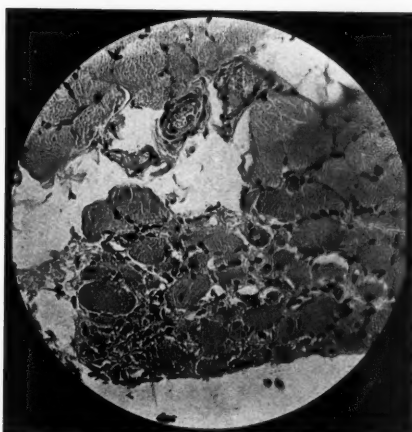


FIG. 5



ACUTE MYELOCYTHAEMIA AND CHLOROMA

BY ALEXANDER GOODALL AND W. A. ALEXANDER

With Plates 10 and 11¹

THE following cases were under observation in the Royal Infirmary of Edinburgh. Case IV was admitted to Professor Edwin Bramwell's ward during holidays and was under the care of Dr. Fergus Hewat, to whom we are indebted for the clinical record.

Case I. A shale miner, aged 29, was admitted on August 19, 1920. He complained of weakness, headache, and a sore mouth of three months' duration.

History. Family history good. Surroundings favourable. He had been in the habit of smoking forty cigarettes a day.

The only previous illness was an attack of tonsillitis in 1906. Present illness followed an attack of influenza which lasted a fortnight. Tonsillitis supervened. The gums became swollen and painful, the teeth tender.

State on admission. Patient muscular. Looked pale and anxious. Temperature 101° F.

Alimentary system. Appetite fair. Patient suffered from thirst. The lips were dry and cracked. There was pyorrhoea, especially around lower teeth. On the gum far back on the left side was an ulcerated mass with a foul odour. The tongue was coated with brown fur.

Haemopoietic system. The lymph nodes in the left submaxillary region were enlarged and tender. No enlargement of glands could be detected elsewhere. The spleen was easily palpated below the costal margin.

Red blood corpuscles numbered 2,600,000 per c.mm. Haemoglobin was 20 per cent. Colour index, 0.4. The red corpuscles were pale and showed deformity and diversity in size. Megaloblasts were present to the extent of 294 and normoblasts 252 per c.mm.

The leucocyte count was 42,000 per c.mm. A differential count showed: polymorphs, 20; large lymphocytes and myeloblasts, 22; small lymphocytes, 3; myelocytes, 52; eosinophils, 1; basophils, 2.

A film taken a few days later showed clearer definition of neutrophil granules, and the differential count was: polymorphs, 24; large lymphocytes, 3; small lymphocytes, 5; eosinophils, 1; myelocytes, 63; myeloblasts, 4.

¹ Part of the cost of the illustrations was defrayed by a grant from the Carnegie Trust.

Circulatory system. The heart was slightly enlarged. There was a soft systolic murmur at all the areas. Pulse, 100. Blood-pressure, 105/95.

Respiratory and nervous systems showed nothing abnormal and the urine contained no abnormal constituent, but some albumin appeared later.

Progress. Patient was treated with a peroxide wash for the mouth and throat. Acetyl salicylic acid and colloidal arsenic were administered internally. There was no improvement. The temperature ranged between 99° and 102°. Patient became progressively weaker and looked more poisoned, and died on August 30.

Section, August 30, 1920 (Dr. P. MacCallum).

There was a little fluid in the right pleural sac and some excess of fluid in the pericardium. There were firm adhesions all over the surface of the left lung. Trachea normal. Lymph nodes at the bifurcation and at roots of the lungs enlarged and pigmented. Both lungs voluminous. Interlobar adhesions present. Scattered subpleural haemorrhages all over surface of right lung. Left covered with organizing fibrin. Both lungs were oedematous and exuded dirty-looking fluid. There were a few scattered patches of broncho-pneumonia.

The heart was enlarged and showed petechial haemorrhages all over the surface. The ventricles were dilated and the muscle was pale. The surface haemorrhages were seen to extend some way into the muscle. The valve cusps were all healthy. The coronary arteries showed some thickening and the aorta showed some atheromatous patches. Blood-clot was paler than normal.

The tonsils were enlarged, firm, and ulcerated. The gums were ulcerated and necrotic looking. The lymphoid tissue at the back of the tongue was hypertrophied. Submaxillary, submental, cervical, prevertebral, and mesenteric lymph nodes were enlarged and rather congested. The thyroid was not enlarged and appeared healthy.

The oesophagus and stomach were healthy. Small intestine was thin and showed a fine injection of vessels in the submucous coat. Peyer's patches were not prominent. The spleen was enlarged to four times the average size. It was pale, soft, and almost diffuent on section. The Malpighian bodies were well seen. Pancreas was swollen and pale with some fibrosis. Liver was enlarged, pale, and firm and gave a very deep Prussian blue reaction. Suprarenals looked normal. The kidneys were rather enlarged. The capsule was not thickened and showed a tendency to strip in layers. Cortical tissue was pale, pyramids congested. Slight iron reaction. Bladder and prostate were normal. Bone-marrow of femur was red almost throughout, but a few pale patches were seen. The bone of the femur was thicker than usual.

Histology. Sections were fixed in formol-alcohol, cut in paraffin, and stained with haematein and eosin, eosin and methylene blue, and by the ferrocyanide method for iron.

Alimentary canal. There were no gross infiltrations.

Liver. The liver cells showed an enormous deposition of pigment, the greater part of which gave the iron reaction. There was an extreme degree of

leucocytic infiltration of the portal tracts extending into the capillaries. In many instances the infiltration was so great that the liver cells appeared in isolated groups of two or three.

Spleen. The Malpighian corpuscles were small and inactive. The pulp showed a uniform invasion of cells corresponding to those seen in the blood. There was a considerable amount of pigment, and a small proportion of it gave the iron reaction.

Kidneys. There was some catarrh of the tubules. The only other change was a slight infiltration of leukaemic cells between the tubules.

Heart. There was slight fatty degeneration of the muscle, and a moderate amount of infiltration with a patchy distribution.

Tonsils. The epithelium was ulcerated and broken up by leucocytes. The lymphoid tissue showed an invasion by granular cells. No germ centres were seen.

Lymph nodes. Structure was lost from leucocyte invasion. There were no germ centres.

Bone-marrow. Sections cut from the femur showed no fat cells. The most abundant white cell appeared to be the myelocyte. Giant cells were very scanty. Films made from a rib showed an enormous preponderance of myelocytes and myeloblasts. There were comparatively few eosinophils and basophils. Nucleated red cells were common, and many megaloblasts were present, and a proportion showed mitotic figures.

Case II. A miner, aged 42, was admitted on April 20, 1922. He complained of shortness of breath and weakness of two and a half months' duration. His family history was satisfactory. He had never suffered from any previous illness of note and his home surroundings were comfortable. Present illness began in January 1922. He had a slight attack of influenza, but returned to work after two days. On February 2 he complained of breathlessness, and this condition with increasing weakness continued. For a fortnight he had been unable to lie down in bed because of dyspnoea. On examination patient was found to be a big powerful man, but showed some wasting. Temperature 98.2° F. He looked seriously ill, very pale and listless. The face had a yellow grey colour and patient was drowsy. The lips were pale, the tongue dry and coated with brown fur. The liver was not enlarged. There were a few moderately enlarged lymphatic nodes on each side of the neck. No other glandular enlargement could be detected. The thyroid was not enlarged. The spleen was found enlarged on percussion, but was not palpable.

The blood showed: red corpuscles, 2,200,000; leucocytes, 94,300; haemoglobin, 35 per cent; colour index, 0.8; polymorphs, 32; myelocytes, 38; large lymphocytes, 20; small lymphocytes, 2; eosinophils, 6; eosinophil myelocytes, 1; basophils, 1.

On staining with Jenner-Giemsa many of the cells classed above as large lymphocytes were distinguished as myeloblasts, but it was found impossible to

make an accurate differentiation between the two since this stain failed to give a satisfactory demonstration of the myelocyte granules. The myelocyte granules were only stained with considerable difficulty, and Jenner's stain applied for half a minute was found the best for the purpose. The red corpuscles showed the usual features of a severe anaemia with the additional presence of a few megaloblasts, and some of these showed mitotic nuclei. The pulse-rate was 104. It was regular, with small volume and low tension. The arterial wall was not thickened. There were no cardiac murmurs. Breathing was rapid and shallow, but no physical signs of disease were elicited. The skin was dry. The urine was acid, specific gravity 1.015, amber coloured. A trace of albumin was found. Patient remained drowsy and listless. He slept at intervals throughout the night, but died the next morning at 9.45.

A post-mortem examination was made by Dr. Sprunt. The pleurae showed a few adhesions but no excess of free fluid. The tonsils were not enlarged, but there was slight excess of lymphoid tissue at the base of the tongue. The glands along the trachea were not appreciably enlarged. The trachea was pale. Lungs showed a little congestion posteriorly. The heart was slightly dilated. The muscle was pale and cloudy but not obviously fatty. There was no valvular abnormality. The liver was pale and slightly enlarged, weighing 1,550 gm. On section it showed fatty degeneration with a rusty brown tinge. The Prussian blue test revealed haemosiderin in very large amount. The gall-bladder was normal and the bile-ducts were patent. The stomach was slightly dilated and there were a few petechial haemorrhages. The pancreas was pale. The intestines showed no haemorrhages or increase of lymphoid tissue. The spleen was enlarged, weighing 240 gm. There was slight perisplenitis. The pulp was diffuent. The Malpighian bodies were indistinct. The kidneys showed a great difference in size. The right kidney weighed only 20 gm. and possessed a very thick capsule. On section there was practically no cortex and the bulk of the tissue was peripelvic fat. The condition was that of arrested development. The left kidney was large and weighed 260 gm. It was pale and the capsule stripped easily. The cortex was increased in width, but the vessels were not distinct. The ureters were patent and the bladder normal. The suprarenal capsules appeared healthy. There was no enlargement of abdominal glands. The bone-marrow as seen in the shaft of the femur showed no alteration beyond one or two small greyish leucoblastic spots. The rib marrow had a uniform grey appearance.

Histology. Stomach and intestine. There was extensive leukaemic infiltration and an increased number of lymphoid nodes in the mucous membrane. The pancreas appeared healthy.

Liver. There was a considerable infiltration of leucocytes into the portal tracts and periphery of the lobules. Here and there the infiltration was so extensive as to break up the liver cells into groups of two or three. Among the leucocytes were a few giant cells of bone-marrow type. The liver cells were atrophic and fatty. Towards the periphery of the lobules they were loaded

with pigment. The ferrocyanide test revealed an enormous deposit of iron in fine granules throughout the liver cells.

Spleen. The Malpighian bodies were small and loosely packed. The pulp showed megaloblasts, normoblasts, myelocytes, eosinophils, and other cells corresponding to those found in the blood. There were also numerous giant cells often arranged in groups. Large areas of the pulp showed endothelial cells, and large lymphocytes packed with erythrocytes in different stages of disintegration. Some of them contained haemosiderin.

Left kidney appeared fairly healthy. There was a slight and irregularly distributed leukaemic infiltration between the cortical tubules.

Right kidney. More than half of the glomeruli were represented by fibrous tissue. There was an enormous dilatation of interlobular arteries and veins. The whole cortex showed a massive leukaemic infiltration. The medulla consisted mainly of fibrous tissue.

Lungs showed anthracosis and fibrosis. The areas of thickened pleura showed great leukaemic infiltration. There was also some infiltration along the bronchial walls. The thyroid showed no change. Bone-marrow from the femur consisted mainly of fat and fibrous tissue, but the grey areas showed the type of marrow seen in the long bones of the rabbit. The preponderating cells were myelocytes and the others corresponded to those seen in the blood. There were numerous megaloblasts. No giant cells were seen in the sections examined. Films from the rib-marrow showed a large number of megaloblasts and normoblasts, myeloblasts, myelocytes, and polymorphs. Eosinophils were numerous. There were very few lymphocytes and basophils.

Case III. An apprentice plumber, aged 16, was admitted on May 9, 1922, complaining of breathlessness; weakness, and spots on the body.

History. About seven weeks before admission patient was working at lead joints in a sewer. While so engaged he began to feel weak and breathless on exertion. His nose bled at intervals for three days, and in a fortnight he gave up work and took to his bed. He noticed spots about the size of pin-heads on his arms, legs, and toes. A week before admission he had a severe attack of vomiting. He described the vomited material as being yellow with streaks of blood. After this attack his eyes became bloodshot and the skin assumed a pale yellow colour. Before the breathlessness began, patient was troubled with constipation and occasional attacks of abdominal pain.

Previous illnesses. Patient stated that he had always been healthy, and had been absent from school for one day only during a period of nine years. Three weeks before his illness began he had a crop of boils on the back of his neck.

Family history. Father and mother alive and well. One brother had rheumatic fever. Home surroundings favourable. He had worked as a plumber for eighteen months, mostly indoors. He had no heavy or unhealthy work till he began making sewer-joints. He smoked an occasional cigarette.

State on examination. Patient appeared well developed. Height, 5 ft. 3 in.; weight, 7 st. 5½ lb. He looked anaemic and his skin had a waxy yellowish appearance. His expression was anxious and he was inclined to be drowsy.

There was dried blood at the nostrils from a recent epistaxis. Intelligence good. Temperature, 102.5° F. Pulse, 128. Respirations, 26.

Alimentary system. Appetite fair. There was occasional pain in the epigastrium, sometimes followed by vomiting. There was a tendency to diarrhoea. Teeth were clean and healthy. The gums were very pale and inclined to be spongy. There was no blue line. The abdomen showed no abnormality beyond a slight increase of liver dullness which extended half an inch below the costal margin in the nipple line.

Haemopoietic system. No enlarged glands could be felt. The spleen was not palpable and not enlarged on percussion. The red corpuscles numbered 1,840,000. Haemoglobin was 25 per cent. Leucocytes numbered 17,800. Of these, polymorphs were 36; myelocytes, 30; large lymphocytes, 23; small lymphocytes, 8; eosinophils, 3 per cent.

Films showed considerable anisocytosis and moderate poikilocytosis. There were numerous megalocytes and a few megaloblasts. Many of the red corpuscles looked unduly plump. Staining with Jenner-Giemsa showed that many of the cells classified above as large lymphocytes were really myeloblasts, but differential counts with this stain were unsatisfactory as it failed in many cases to demonstrate the neutrophil granules.

Circulatory system. The heart was slightly enlarged. A blowing systolic murmur could be heard at all the areas.

The respiratory system showed nothing of note.

Nervous system. Patient was drowsy and slept a great deal. He had occasional headaches. The knee-jerks were brisk. The pupil reactions were normal. Optic disks pale. The urine showed an acid reaction, sp. gr. 1.015, no abnormal constituent. The skin was pale and slightly yellow and felt moist. A few faded petechiae could be seen on the legs.

Progress. Patient was put on light diet and liquor arsenicalis was administered in doses of three minims thrice daily. The temperature fell to 99° the day after admission, and never exceeded this figure again till the day before he died, when it reached 101°. On May 10 the faeces showed a positive benzidine reaction for blood. On the 14th and 17th he had slight attacks of epistaxis. On the 27th his red cell count had fallen to 850,000 per c.mm., haemoglobin to 20 per cent. Leucocytes were then 19,400. On the 29th enlarged glands could be detected in both groins. On June 1 vomiting began and recurred almost daily. Patient died on June 9.

A post-mortem examination was made on June 9 (Dr. Alexander). The body was obviously anaemic. The general development was good for the age and the body was well nourished. There was no oedema. There were a few petechiae in the skin, the most recent being at the root of the neck. The body fat was of a pale primrose tint. The gums showed a slight sponginess. The pharyngeal

lymphoid tissue was prominent. The tonsils showed nothing of note. The thyroid gland looked healthy. The thymus gland was easily recognizable but not readily defined. The larynx was healthy. The pleural sacs showed no excess of fluid and no adhesions. The lungs showed a few small haemorrhages under the pleura. The right lung on section showed numerous haemorrhagic areas in all the lobes. There was no obvious bronchitis. The left lung appeared healthy.

Heart. There was no pericarditis. There were a few subepicardial petechiae. The heart showed slight hypertrophy of the left ventricle. The valves were healthy, but the myocardium next the interior showed early fatty change.

The oesophagus showed nothing of note. The peritoneal sac was healthy, the stomach was of average size and appearance, the intestine did not contain blood. Its lymphoid elements were not unduly prominent.

The liver was rather small, weighing 1,100 grm. It had a rusty brown colour and gave an intense Prussian blue reaction.

The pancreas appeared healthy. The spleen was small and was only two-thirds of the average adult weight. Its lymphoid nodules were just visible.

The suprarenals were of the usual size and appearance. The kidneys showed no chronic disease. They were rather pale and gave a moderate haemosiderin reaction. The lymphatic glands in general showed slight enlargement. There were numerous red haemolymph glands in different parts of the body. The para-aortic glands were considerably enlarged, and in connexion with several of these lying on the right side there was a growth closely attached to the periosteum covering the body of the third lumbar vertebra. This growth was tough and firm and of a bright green colour, which faded on exposure to the air. It appeared to be of the nature of chloroma.

The inguinal glands were distinctly enlarged and had a white centre and more fleshy-looking and semi-translucent peripheral part. Some of these glands showed a tinge of green colour. The bone-marrow was of a uniform pale red colour.

Histology. The stomach showed areas of leukaemic infiltration of the mucous membrane. Small intestine showed similar infiltrations round the glands. The Peyer's patches showed fairly numerous germ centres.

Liver. There was a moderate infiltration in the portal areas. The cells showed little change beyond a copious deposit of pigment, most of which gave the Prussian blue reaction.

Spleen. The Malpighian corpuscles were small and inactive. The pulp showed moderate cellular activity. The majority of the cells were myelocytes and large lymphocytes. There were a few giant cells of bone-marrow type. Pigment was rather scanty. Most of it gave the iron reaction.

Kidneys showed slight post-mortem autolytic changes. There was congestion especially of the medullary vessels. Some pigment was present in the convoluted tubes and ascending limbs of Henle's loop. Heart-muscle showed slight fatty degeneration and there was a moderate degree of leukaemic infiltration between

the fibres, with a very patchy distribution. The right lung showed terminal oedema and haemorrhages.

The thyroid gland showed no obvious change. The thymus showed a moderate amount of replacement by fat. There was evidence of delay in the involution of the Hassall's corpuscles, which were numerous and large, consisting in many cases of areas of necrotic cells not showing the concentric arrangement seen in the adult. The suprarenals appeared normal. In the surrounding fat there was a diffuse leukaemic infiltration. Most of the cells were myelocytes, and there were cells showing the structure of bone-marrow giant cells.

Aortic glands and tumour. Sections showed the gland structure fairly well maintained. There were no germ centres. The lymph paths were, for the most part, filled with cells larger than the lymphocytes of the follicles, with vesicular nuclei and the general characters of myelocytes. The capsule was densely infiltrated with similar cells, so that its outline could just be followed. The infiltration became less dense as it extended into the surrounding fat, and there the appearance resembled bone-marrow. The infiltration extended between the fibrous tissue strands of the periosteum of the lumbar vertebra to which gland and tumour were adherent. In addition to the myelocyte infiltration there were areas in the lymph paths and in the surrounding fat where cells resembling bone-marrow giant cells were present, and the appearance suggested that the whole lymph node might have been a new formation. Haemolymph glands showed much the ordinary appearance except for a lack of definition between gland structure and fat, the one appearing to invade the other. There was slight phagocytic activity and germ centres were fairly numerous.

Bone-marrow. Sections from the femur showed an almost complete disappearance of the fat cells. There was a nearly uniform distribution of red cells, neutrophil myelocytes, and a few eosinophil myelocytes.

Every here and there were erythroblastic areas which appeared unusually circumscribed. The cells showed great mitotic activity. Giant cells were scanty and small. There were masses of golden pigment in the endothelial cells. Film preparations showed similar changes, but there was in addition a fair sprinkling of basophils whose granules had evidently not been conserved in the sections.

Case IV. Male, single, aged 36, admitted on September 2, 1922. Patient had complained of pain in both hips for five weeks, and for a week before admission had suffered from facial paralysis on the left side, followed three days later by facial paralysis on the right side.

History. For several weeks patient had been conscious of vague pains in his feet and lower limbs. Four weeks before admission the pain suddenly became much more severe and seemed to affect the sciatic nerves, especially the right. On August 17 patient found when he woke up that he was suffering from facial paralysis on the left side, associated with some pain and tenderness in front of the ear. Three days later paralysis of the right side of the face occurred with similar suddenness. He next began to feel pain in the left side of

the chest, and on the recommendation of Dr. Caldwell, of Leith, he was admitted to hospital.

Family history was good. Patient had apparently led a vagrant life, disappearing from home for days and sleeping out in fields. There was no history of alcoholism. He served in the army during the war and was discharged with a pension in 1919 for melancholia. He had done no work since. The only previous illnesses he could remember were an ulcerated leg and an attack of jaundice.

State on admission. There was facial paralysis on both sides. Face pasty and sallow. Patient looked 'toxic' and sweated profusely. He was truculent and discontented. Temperature, 98° F.

Nervous system. Patient was depressed and sulky, and his intelligence seemed defective.

Cranial nerves. Smell not impaired. Sight good. Optic disks normal. No squint or nystagmus. Slight ptosis on left side. Pupil reactions normal. There was complete facial paralysis on both sides. The lips did not move on speaking. Facial muscles did not respond to faradism. Contraction to galvanism was very slow. K. C. C. was slightly greater than A. C. C. There seemed to be some impairment of taste in the anterior two-thirds of tongue, but this was uncertain, owing to the patient's stupidity and unwillingness to help. Hearing was impaired on both sides, but there was no evidence of aural disease.

There was no wasting nor tremor of the tongue. There was no impairment of muscles apart from the face. The plantar reflex response was flexor. The knee- and ankle-jerks were slight and sluggish. The bowels and bladder were evacuated in bed, but it could not be determined whether this was due to impairment of reflex or mental function. Patient complained of frontal headache and pain in the chest, but sensibility was unimpaired as far as could be determined. Patient disliked movement and complained of pain on sitting up or leaning forward.

Respiratory system. Rhonchi could be heard all over the chest except at the base of the right lung, where there was evidence of a small fluid effusion.

Circulatory system. The heart seemed slightly enlarged. There were no murmurs. Pulse, 104, regular. Systolic blood-pressure, 130.

Alimentary system. The teeth were very dirty. The tongue was coated and the breath foul. The liver was enlarged, being 1 in. below the costal margin in the nipple line.

Haemopoietic system. There were no definitely enlarged glands although the neck was thickened. The spleen was considerably enlarged.

The blood gave a negative Wassermann reaction. The red corpuscles numbered 3,200,000. Haemoglobin was 55 per cent. The corpuscles showed a moderate irregularity in size and shape, and an occasional normoblast was noted. Leucocytes numbered 57,000 per c.mm. A differential count showed: polymorphs, 20; large lymphocytes, 7; small lymphocytes, 16; eosinophils, 1; neutrophil myelocytes, 45; eosinophil myelocytes, 1; myeloblasts, 10.

Urinary system. Urine was acid, sp. gr. 1,018. There was rather more than a trace of albumin.

Progress. On September 6 the temperature rose to 99.5° F., the dullness over the right base had increased, and eight ounces of blood-stained fluid were drawn off. The fluid contained numerous red blood corpuscles and numerous leucocytes corresponding to those found in the blood. Many of them were vacuolated and degenerated. Patient became rapidly and progressively worse. The respirations became hurried and there was evidence of fluid accumulation in both pleurae. There were copious sweats, and on September 10 the temperature rose to 100°. Patient died next day.

A post-mortem examination was made on September 11 (Dr. Alexander). The skull and brain showed no abnormality. The neck appeared broad. The cervical glands were large and discrete. High up in the pterygoid regions and in close relationship with the parotid glands on both sides were greenish tumour masses of fleshy consistency. The exact relationships of the tumours in these regions were not determined, but it seemed probable that the facial nerves were involved in them. The tonsils were of average size. The lingual tonsil was prominent. The thymus was not recognized. The thyroid appeared healthy. The larynx and oesophagus showed no gross abnormality. The pleural sac on the right side contained much blood-stained fluid. The whole pleural surface, visceral and parietal, was thick and fleshy and of a dull, dirty greenish tinge. On the left side there was a quantity of serous fluid, and the pleura was thickened irregularly by plaques of tissue similar to that described on the right side. The lungs were collapsed. There was no pneumonia nor tumour infiltration. The mesenteric glands were slightly enlarged. They exhibited a slight greenish colour on section. The heart and aorta were of normal size and appearance.

There were flat plaque-like masses on the inner aspect of the chest on the right side, on the inner aspect of the sternum, and on the outer aspect of the left costal cartilages close to the episternal notch. These masses were adherent to the periosteum but did not invade bone. They infiltrated and replaced muscle tissue. On section they presented an opaque whitish-green appearance.

The spinal column presented striking features. There was a continuous nodular infiltrative tumour growth of a greenish colour lying in front and on each side of the spine, separating the aorta from the vertebral column. This growth was firmly adherent to the periosteum but did not involve bone. It was most evident in the thorax and was adherent to the left lung on its mesial aspect near the apex. The peritoneum was healthy. The stomach was rather thickened. The intestine showed no unusual prominence of lymphoid tissue. The mesenteric glands were not enlarged. Those of the gastro-hepatic omentum and in the region of the head of the pancreas were considerably enlarged and had a green colour on section.

The liver weighed 75 per cent. over the average. There was a tumour-like infiltration along the portal tracts. This was green in colour. The gall-bladder and ducts appeared healthy. The pancreas seemed normal. The spleen was

four times the usual size. There were no adhesions or infarcts. It was firm in consistency, cut clean, and had a uniform dark colour. The Malpighian corpuscles were not visible. The suprarenals, bladder, and ureters showed nothing of note. Both kidneys showed small green tumour masses scattered through the cortex. The largest were about the size of a split pea. The bone-marrow of the femur and ribs showed a diffuse leucoblastic reaction, with a greenish tinge appearing in small patches.

Histology. Liver. The liver cells showed no important change. There was no iron reaction. Apart from the excess of leucocytes in the capillaries there was less diffuse leukaemic infiltration than is commonly met with, although a certain amount was present in all the portal tracts. Many of the tracts, however, showed a massive infiltration. These infiltrations appeared to have caused a wide separation of the large vessels and ducts, and in the infiltrating tissue there were small vessels, capillaries, and lymphatics, many of which seemed to be of new formation. There also appeared to be an extensive proliferation of the bile-ducts in the leukaemic areas.

Spleen. The Malpighian bodies were small and inactive. The pulp was uniformly packed with leukaemic cells. These were myelocytes, myeloblasts, polymorphs, and eosinophils, some large lymphocytes, and a few nucleated red cells. There were a few giant cells. A considerable amount of golden yellow pigment was present in endothelial cells, large lymphocytes, and free in the pulp.

Kidneys. The greater part of the sections showed no great change, but the small green tumours were seen to consist of leukaemic areas invading the capsule. These formed dense masses on the surface and extended into the cortical labyrinth between the convoluted tubules for a considerable distance. *Lungs* were healthy except for a certain amount of anthracosis and a slight degree of peribronchial leukaemic infiltration.

Pleura. The pleura was enormously thickened. The superficial layer consisted largely of granulation tissue. The deep layer showed a continuous leukaemic infiltration about 1 mm. in thickness. The cells were of the types already described. There were also a few giant cells of bone-marrow type. The infiltrated areas showed numerous wide capillaries, small blood-vessels, and lymphatics.

The thyroid showed nothing of note.

Muscle. Sections of the erector spinae showed a massive leukaemic infiltration which invaded the epimysium and perimysium, and in many places separated the individual muscle fibres. Parts of the muscle appeared to be atrophied and replaced by granulation tissue.

Lymph nodes. Except for the presence of a few small and inactive follicles these showed a uniform appearance due to a leukaemic infiltration.

Bone-marrow. Sections were cut from three different portions. In only one of these were any fat cells left. One set of sections showed a uniform appearance except for the presence of a few bony spicules. The preponderating cells were myelocytes. Eosinophils were numerous, and there were many

normoblasts. Giant cells were scanty and small. There were no cells showing phagocytosis of red and white cells as is commonly seen in lymphatic leukaemia, but a few scattered granules of golden brown pigment, both intra- and extra-cellular, were seen.

In some of the sections there were areas about the size of a low-power field showing necrotic changes with a remarkable degree of karyorrhexis in both red and white cells. In some instances the nucleus was broken up into ten portions.

Tumour masses. The structure of these did not differ materially from that of the leukaemic infiltrations in the organs. Sections cut from the large pre-vertebral mass at the lower end of the aorta showed infiltration of the deep layers of the parietal peritoneum. This extended into a large mass surrounding vessels and nerves. In several parts the infiltration had left groups of fat cells giving an appearance resembling very cellular bone-marrow. Towards the interior the tumour tissue was more dense, the cells were more uniform and showed a certain amount of arrangement in rows along delicate strands of fibrous tissue.

Comments. Case I. This is a typical case of acute myelocythaemia. The only point to which attention need be called is the pathologist's remark regarding the thickness of the bone. One of us (1) has previously called attention to the association which rarely occurs between leukaemia and osteosclerosis, and if this case may be taken as an example it is apparently only the fifth to be recorded.

Case II. This case was even more acute, and while the rib marrow showed leukaemic change throughout, the marrow of the femora showed only small reddish-grey patches. This case also showed mal-development of one kidney, and this kidney contained an extensive leukaemic infiltration which was practically absent from the other.

Both of these cases might justify a diagnosis of leukanaemia, if such a term were necessary or desirable.

Case III. This case is of surpassing interest inasmuch as it presents an intermediate stage between leukaemia and chloroma, and, so far as we have ascertained, it appears to be unique. Another interesting feature was the small size of the spleen and a great activity on the part of the haemolymph glands.

Case IV. This is a typical case of chloroma. A case with paralysis of one facial nerve has been recorded (2), but we have found no previous instance of chloroma with double facial paralysis. In the organs there were areas which suggested embolic lesions probably caused by leucocytes.

Discussion.

Incidence of acute myelocythaemia. All four cases are examples of myelocythaemia in acute form, the duration according to the patients' statements varying from two weeks to three and a half months. In 1912 one of us (1) published

a case which at one time appeared to be the twentieth on record. Since that time a considerable number has been added. A recent one, that of Fleming and Davidson (3), is of special interest on account of the large number of leucocytes showing mitoses in the circulating blood. The number of cases of chloroma hitherto published is still under 100—probably in the neighbourhood of 80.

Blood changes. All the cases presented the relatively low leucocyte counts usually associated with the more acute examples of the disease. A point of importance was the difficulty in demonstrating neutrophil granules in the myelocytes. In two of the cases, before we had seen them, the house physicians had arrived at a diagnosis of acute lymphatic leukaemia by including a number of cells which were really myelocytes in their lymphocyte counts. Even on this reckoning the percentage of non-granular cells was not sufficient to warrant a diagnosis of lymphatic or myeloblast leukaemia. In these conditions the percentage of non-granular cells is rarely less than 90, and, in our experience, never under 80.

Such cases as these provide an argument that the myeloblast or lymphoidocyte of Pappenheim is a cell differentiated as the precursor of the myelocyte and not the immediate parent of either myelocyte or lymphocyte.

With one exception (4) which we regard as doubtful, no case of leukaemia showing an excess of both lymphocytes and myeloblasts has ever been published, while myeloblasts are present in every case of myelocythaemia.

The low number of red corpuscles in all the cases is regarded as the result of the crowding out of the erythroblastic elements by the excessive proliferation of white cells in the marrow. The presence of megaloblasts and normoblasts is probably due to the disturbance so caused, and possibly to toxæmic changes in the marrow.

Deposits of haemosiderin. The large amount of iron present in the liver in three of the cases, and to a less extent in the spleen and haemolymph glands, is readily explained if these be regarded as the normal haemolytic and blood-filtering organs, and haemolysis is active because a poor quality of corpuscle is turned out by the marrow, and because the capillary circulation is slowed by the abnormal number of leucocytes in the blood. Tait and MacCartney (5) showed that after the injection of Indian ink into the blood the maximum amount of blackening occurred in these organs. Muir and Dunn (6) have also shown that when enough of a haemolytic serum is injected to destroy more than one-half of the blood within three days, nearly all of the blood so destroyed is deposited in the liver and spleen and may overflow into the kidneys.

It has never been suggested that in leukaemia there is any exaggeration of active haemolysis in the portal system, and such observations and cases as those quoted go far to oppose the view that the deposits of iron in pernicious anaemia have any special significance indicative of toxic processes in the portal system. Incidentally, we may remark that such theories fail to explain the deposit of iron in the haemolymph glands and other situations throughout the body in pernicious anaemia.

Other changes in the organs. The comparatively small size of the spleen was a feature of all the cases, but splenic enlargement is probably proportionate to the chronicity of the case.

A point of interest is the tendency towards the leukaemic invasion of pathological tissue as evidenced in the mal-developed kidney in Case II, and in the thickened pleura in Cases II and IV.

The endogenous purins and pigment. We have made no special observations in regard to these. They are doubtless matters of interest, but we feel that the elucidation of the condition will not emerge in these directions. Cases of leukaemic tumours without the green colour have been described (7).

Two cases of leukaemic infiltration of the bronchi giving a green colour to their walls and to the exudation have been reported (8). Shennan was able to restore the green colour in Dunlop's case (13) after it had faded by treatment with reducing agents, and Hall, Hebb, and Bernstein (2) found that the colour was bleached by peroxide of hydrogen.

On the other hand, Trevithick (9) was able to restore the colour by the application of peroxide of hydrogen. Gulland and Goodall (10) were able to confirm this observation in one case and not in another. Pope and Reynolds (19) worked out the solubility of the pigment in a number of reagents and concluded that it was a fatty pigment combined with iron.

Chloroma and its relationships. The first case of chloroma was reported by Allan Burns in 1823 (11). Only a few instances were reported until Dock (12), Melville Dunlop (13), and Byrom Bramwell (14) described cases and established its connexion with lymphatic leukaemia. It is now known to be associated with all varieties of leukaemia. One aleukaemic case has been reported (15), but this has probably no greater significance than the occasional occurrence of non-chloromatous cases of leukaemia with low white cell counts which are usually readily explicable. We wish to emphasize the importance of Case III as illustrating an intermediate condition between acute myelocytic leukaemia and chloroma.

The overgrowth of leukoblastic tissue which occurs in leukaemia appears to be useless, and strongly suggests a process more closely allied to tumour growth than any other condition. The existence of chloroma is a strong argument for this view. Gulland and Goodall (10) arrived at this conclusion, adducing, among others, the following reasons: 1. The ordinary channels of infection and chemiotactic stimulus are those least consistently affected by the leukaemic infiltration. 2. Leucocyte infiltration occurs in tissues and organs little likely to be the source of chemiotactic stimulus. 3. The infiltration is greatest in the most chronic cases—a condition just the reverse of the results of known chemiotaxis. 4. Symptoms are alleviated by removal of the infiltration by the application of X-rays.

We adhere to these views, but at the same time we admit the possibility that both leukaemia and many forms of malignant disease may yet be found to be the result of an infection which differs in its results from those of known

animal and vegetable parasites. No one who has seen many cases of leukaemia, especially in acute form, can fail to be impressed by the frequency of a history of gum-boils, tonsillitis, or similar affection, and the common incidence of inflammatory affections of mouth and throat, and the frequent occurrence of fever with or without complications.

Such a history is noted in the four cases we present. On the experimental side it is known that cancerous material injected into mice may cause a condition closely resembling myelogenous leukaemia, and James Young (16) has offered evidence that this result may be the effect of microbic action.

Ellermann (17) has shown that leukaemia can be transmitted in fowls by experimental injection, and has been able to pass a recent strain through 12 generations. Most of the cases were myeloid, but a lymphatic case has been observed.

The virus was found to be filterable. The inoculation of human leukaemic material into fowls had given negative results.

We are in agreement with Ewing (18) that the aetiology and pathology of tumours has been obscured by the attempt to classify a number of totally different conditions into too definite groups.

Be this as it may, we suggest as something more than a mere speculation that leukaemia is closely allied to a malignant process, that both leukaemia and malignant disease may yet prove to be the result of infections, and that the former offers to the bacteriologist and pathologist a field for investigation which has never yet been adequately exploited.

Summary.

Cases are described as tabulated below:

Case.	I.	II.	III.	IV.
Age	29	42	16	36
Temperature (average)	101°	98°	102°	98°
Duration (months)	3½	3	3	½
Red corpuscles (millions)	2.6	2.2	1.8	3.2
Leucocytes (thousands)	42	94	17	57
Myelocytes (per cent.)	63	38	30	45
Size of spleen	× 4	× 2	× ½	× 4
Iron in liver	+	+	+	0

Previous illnesses were influenza and tonsillitis, influenza, boils, and ulcerated leg, and other features were possible osteosclerosis, an undeveloped kidney showing leukaemic infiltration, a single chloromatous tumour, and frank chloroma in the four cases respectively.

The relationships and pathology of leukaemia and chloroma are discussed.

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DESCRIPTION OF PLATES.

PLATE 10, FIG. 1. *Case IV.* Section through dorsal vertebra showing tumour mass surrounding body and separating it from peritoneum and aorta.

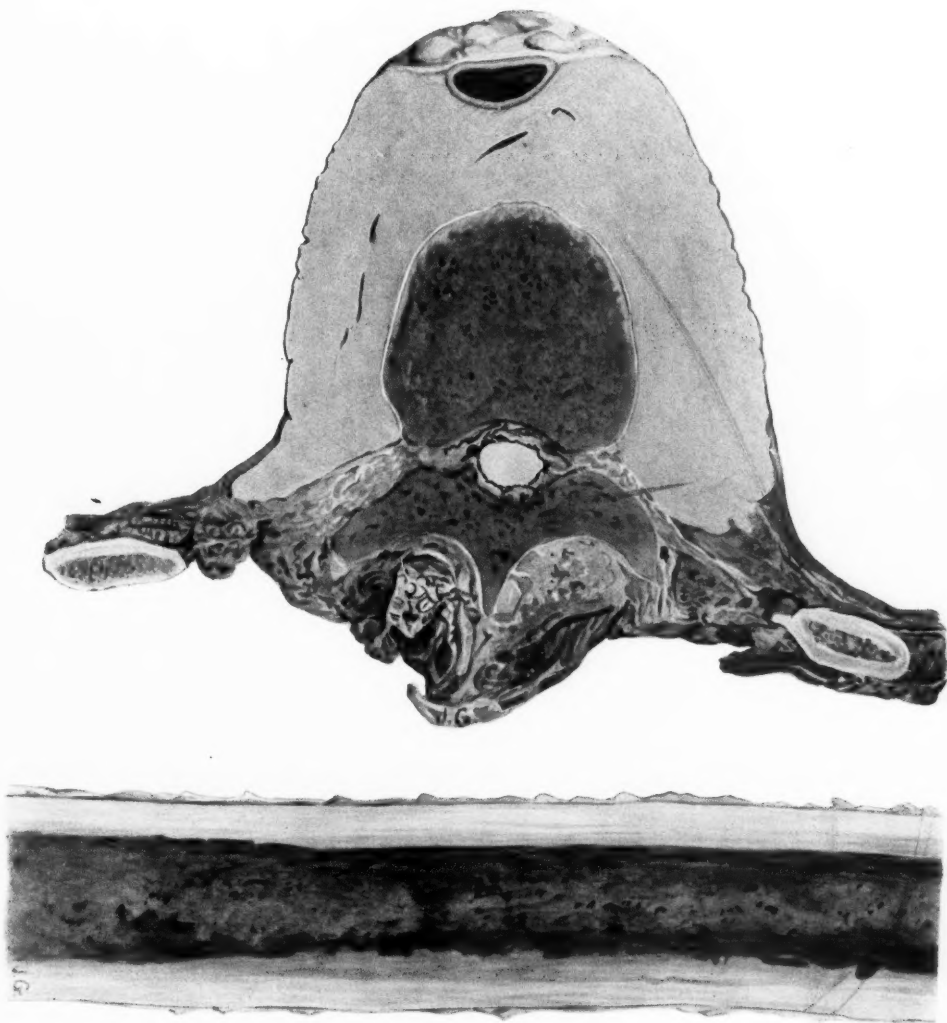
FIG. 2. *Case IV.* Longitudinal section of femur showing marrow.

PLATE 11, FIG. 1. *Case III.* Para-aortic lymphatic gland (right) with tumour growth (left) connecting it to periosteum of lumbar vertebra. $\times 45$.

FIG. 2. *Case IV.* Visceral pleura of right lung showing (from above downwards) exudate, granulation tissue, tumour tissue, deep layers of pleura and lung. $\times 30$.

FIG. 3. *Case IV.* Erector spinae muscle and fat showing infiltration and destruction by the tumour. $\times 75$.

FIG. 4. *Case IV.* Bone-marrow showing eosinophil and neutrophil myelocytes and tumour cells (myeloblasts). $\times 1,000$.





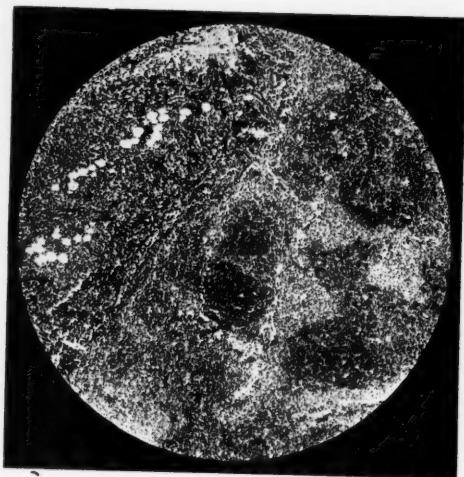


FIG. 1

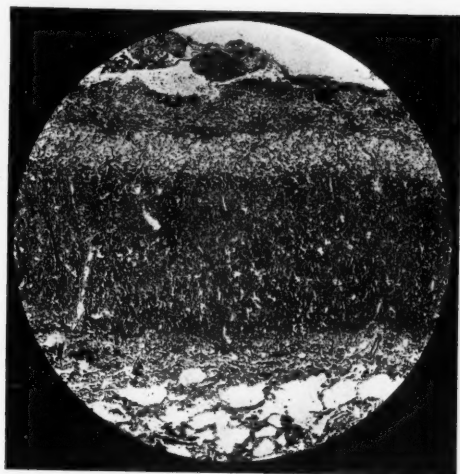


FIG. 2

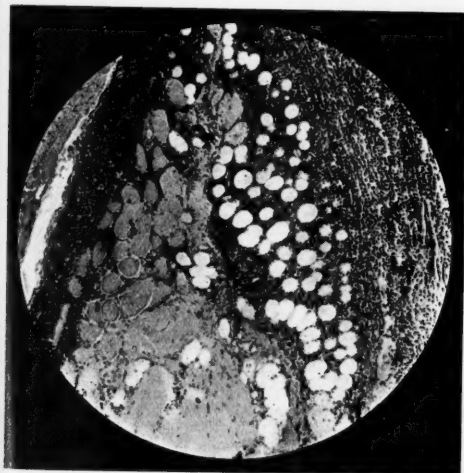


FIG. 3

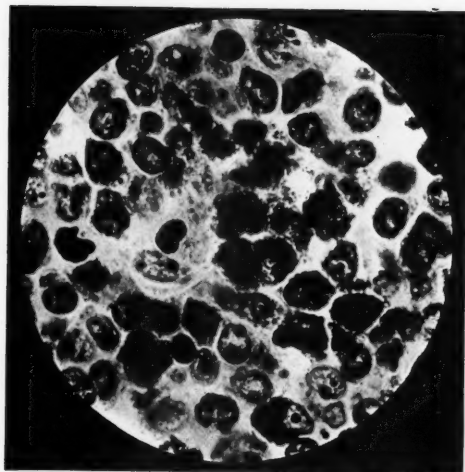
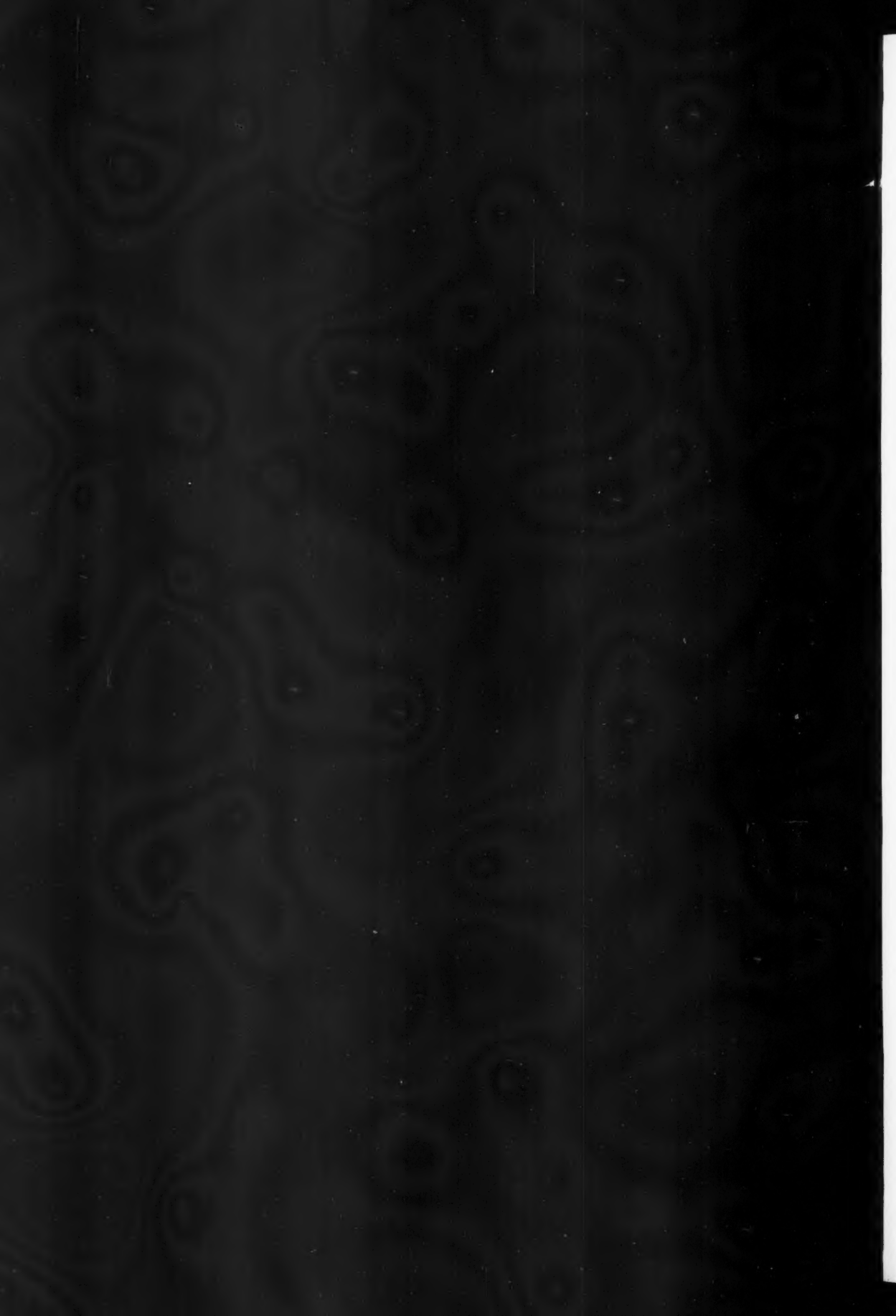


FIG. 4



AN INVESTIGATION INTO THE PATHOGENESIS OF DISSEMINATED SCLEROSIS¹

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With Plates 12 and 13

THE following paper is based on work done during the last three years on the aetiology of disseminated sclerosis. The investigation has been carried out along clinical, therapeutic, serological, and experimental lines. The closest co-operation between clinical observation and laboratory investigation has been aimed at throughout.

Historical Note.

The first record of disseminated sclerosis in the literature is by Cruveilhier (1) (1842), in his *Atlas d'anatomie pathologique*, in which the lesions are figured. The first clinical study is by Frerichs (2) (1849). The disease was made widely known by Charcot (3). Dawson (4) (1916), in continuation of the work commenced in conjunction with Bruce, placed the morbid histology of the disease on a sound pathological basis, and concluded that we may be dealing with 'the production of a specific metabolic disturbance due to a latent organism or an auto-intoxication'. He emphasized the view that future investigation should be along bacteriological, serological, and experimental lines.

Clinical Features.

Disseminated sclerosis would appear to be a disease of more common incidence than has been recognized in the past, and an outstanding feature of the cases considered in the present series is the frequency with which the significance of the earliest symptoms has been overlooked. A disease in which the morbid pathology consists of plaques of sclerosis distributed in an irregular and apparently haphazard fashion throughout the brain and spinal cord must of necessity vary widely in

¹ A report to the Medical Research Council.

its clinical manifestations, and yet the almost constant presence of a combination of the so-called cardinal signs is a striking phenomenon. In this respect the disease resembles syphilis from the fact that certain parts of the nervous system seem to be specially prone to be attacked.

Types. Our own series of cases appears to fall into two groups. In the first group the more acute type is encountered. The victim is usually a young and otherwise healthy adult under 30 years of age. A preceding history of trauma or acute exanthem has been obtained in the majority of cases, an aspect of the disease which has been emphasized by nearly every observer. Due weight must be given to the fallacy of 'post hoc, ergo propter hoc', but the association of such a history is so frequent that these factors cannot be totally disregarded. The lowering of local or general resistance may be a possible explanation. The cases included in this group more or less rapidly assume the classical form of the disease. In the second group the patients attacked are usually somewhat older. The disease has more of a spinal than of a cerebral distribution: its onset is more gradual and its clinical course more slowly progressive. It is this group which presents the greatest difficulty in diagnosis, as syphilis and arterio-sclerosis have to be excluded. These cases do not, in our experience, tend to develop the established picture of classical disseminated sclerosis.

Early Manifestations.

From a study of the clinical histories of patients suffering from the fully-established disease it is obvious that they have passed through a stage in which they have shown symptoms which seem to be almost as unmistakable as the later signs of permanent damage. The clinical manifestations of the established disease are less capable of misinterpretation and need not be further referred to here. The person attacked is almost invariably of the sympathetico-tonic type, and is usually described by relatives as having been 'highly strung' in childhood. It is not clear whether this is an early manifestation of the disease or whether it is an indication that disseminated sclerosis is implanted on a neuropathic soil. The earliest definite evidence of the disease consists of one or more of three main groups of symptoms: (1) ocular manifestations; (2) evidence of lumbar involvement; (3) paraesthesiae.

1. *The early ocular manifestations of disseminated sclerosis.* These show themselves by deranged function of the ocular muscles and by disease of the optic nerve itself. Diplopia, usually of a transient type, is present in a considerable proportion of cases. A patient presenting such a history should never be dismissed without further investigation, which should include a thorough clinical and serological examination. The ocular defect in many such cases can be demonstrated only by clinical tests. A loss of balance of the external ocular muscles is frequently present, and in well-marked cases this gives to the eyes a more or less characteristic appearance. Other common causes of diplopia, such as neurosyphilis or high refractive error, must, of course, be excluded. It is

doubtful if it ever be justifiable to regard a demonstrable diplopia as functional in origin.

As regards the optic nerve, temporary obscurity of vision of one or both eyes is frequently encountered in the earliest stages. The basis of this symptom lies in the existence of a retrobulbar neuritis, the clinical detection of which establishes beyond doubt that a pathological process is present. For example, in a case in our series, a patient developed retrobulbar neuritis of one eye in 1914, the second eye becoming similarly involved six months later. The eye symptoms rapidly cleared up, and six years elapsed before frank disseminated sclerosis became established. Idiopathic retrobulbar neuritis occurring in a young adult is highly suggestive of disseminated sclerosis, and at this stage every endeavour should be made to establish a definite diagnosis. If no other cause for the condition can be ascertained it is open to question whether a diagnosis of disseminated sclerosis is not justifiable.

2. *Early evidence of lumbar involvement.* Evidence of involvement of the lower spinal segments of the cord is shown by derangement of bladder function (frequency, precipitancy, hesitancy, and occasional incontinence and retention) and frequent nocturnal seminal emissions. This syndrome, in common with the other symptoms of the disease, may, and frequently does, completely clear up.

3. Paraesthesiae are extremely common, but, owing to the mental condition of the patient, are more difficult to assess as regards their exact significance in the diagnosis of the disease. Their coexistence with a history of temporary 'uselessness' of a limb should be regarded with suspicion.

The Serological Features of the Disease.

The main purpose of a serological investigation is to exclude syphilis. In the present series a routine examination comprising the Wassermann reaction of the blood and cerebro-spinal fluid, the cell count, the protein content, and the colloidal gold reaction of the cerebro-spinal fluid has been carried out.

1. *The Wassermann reaction.* Any case showing a positive Wassermann reaction in the blood or cerebro-spinal fluid has been provisionally regarded, for purposes of classification, as not being true disseminated sclerosis. It must, however, be concluded from a study of the case recorded by Perdrau and Stebbing (5) that a positive Wassermann reaction in a case of disseminated sclerosis does not necessarily mean that the basis of the pathological condition of the nervous system is syphilitic.

2. *The cell count* of the cerebro-spinal fluids, as estimated by the Fuchs-Rosenthal chamber, is, in our series, within normal limits.

3. *The protein content* of the cerebro-spinal fluid estimated by the ammonium sulphate tests (both Ross Jones and Nonne-Appelt), and also by Noguchi's (6) lipoidal flocculation method, has not been found to be increased.

4. *The colloidal gold reaction.* This test has been applied over a wide series of nervous diseases, and approximately 2,000 reactions have been carried out.

The reaction is not specific in the sense that its occurrence is confined to a particular disease. It gives singularly constant positive results in neurosyphilis, disseminated sclerosis, and encephalitis lethargica. Anomalous curves are occasionally encountered in other conditions, the pathological basis of which is, however, often not clear. The reaction is, therefore, of no value in the attempt to differentiate between disseminated sclerosis and neurosyphilis, but is of considerable significance in differentiating between functional nervous disorders and early disseminated sclerosis. This we would regard as one of its most important functions. It also possesses considerable value as a means of registering results of treatment. Thus, in a large series of cases of neurosyphilis under intensive treatment with salvarsan, a progressive modification in the direction towards negative of the colloidal gold reaction has been observed. Such modification has been noted to accompany a fall in the cell count and in the protein content where previously these had been in excess of normal. In cases of disseminated sclerosis treated by salvarsan similar modifications have been found to occur.

In view of the difficulty of preparing and standardizing colloidal gold sols, of our ignorance of the exact nature of the reaction, and of its non-specific character, one must conclude that, although the test is of value in the investigation of disseminated sclerosis, the information which it yields is limited.

The Question of the Relationship of Syphilis and Disseminated Sclerosis.

There are many striking analogies between disseminated sclerosis and neurosyphilis. The similarity of the ocular manifestations in respect of diplopia and optic atrophy is striking, and the vast majority of cases showing clinical manifestations of spinal sclerosis fall under the heading of one or other of these two diseases. It is of interest to note that in another known spirochaetal disease, viz. East African relapsing fever, Manson and Thornton (7) state that the 3rd, 4th, and 6th nerve lesions are encountered.

A causal connexion between the two diseases was first advocated by Jacobsohn (8), and has found more recent support from Byrnes (9). In the majority of cases the age incidence is against such a connexion, the victim of disseminated sclerosis being typically free from any history or evidence of syphilis either congenital or acquired. Occasionally syphilis may so closely simulate disseminated sclerosis that the two diseases are clinically indistinguishable, and for the differential diagnosis it is necessary to depend upon the Wassermann reaction.

The Infective Nature of Disseminated Sclerosis. Experimental Transmission.

The conception of disseminated sclerosis as an infective disease was first put forward by Marie (10) in 1891, and the original suggestion that a spirochaete might be the infecting organism appears to have come from Buzzard (11) in 1911. The pioneer work in connexion with the transmission of disseminated sclerosis to

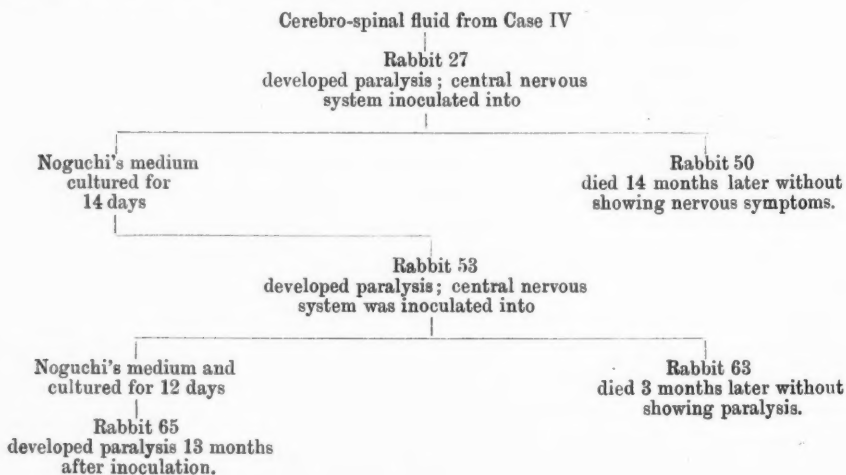
animals was done in 1913 by Bulloch (now Gye) (12), who, by injecting rabbits with cerebro-spinal fluid from a case of the disease, was able to produce a condition of paralysis and demonstrated degenerative changes in the spinal cords of the animals. He concluded that disseminated sclerosis was caused by a filter-passing organism or by a water-soluble poison. Siemerling and Raecke (13) (1914) injected two monkeys and several rabbits with cerebro-spinal fluid, but with negative results.

Kuhn and Steier (14) (1917) injected blood and cerebro-spinal fluid into guinea-pigs and rabbits, and claim to have passed on the disease through a series of four guinea-pigs and of two rabbits; spirochaetes were demonstrated in the heart's blood and in the vessels of the liver. In March 1917 these authors inoculated a monkey; the fate of this animal is given in a later publication (15) (1920). In February 1918 it developed a fleeting paralysis, which disappeared, but reappeared in June 1918. The animal was killed in July 1918, and in the cerebrum there were found foci characterized by patchy destruction of the medullary sheaths. This is the first case recorded in the literature in which a condition of paralysis was produced in *Macacus rhesus* by means of inoculation with cerebro-spinal fluid from disseminated sclerosis. Marinesco (16) (1919) produced paralytic phenomena in two guinea-pigs following intracerebral injection of cerebro-spinal fluid. The cerebro-spinal fluid obtained from the 4th ventricle of these animals showed numerous spirochaetes. Rothfeld, Freund, and Nornowski (17) (1921) inoculated rabbits and guinea-pigs from four cases of disseminated sclerosis. They produced paralytic symptoms in some of the animals. They failed to find spirochaetes, and rejected the conclusion that they had transmitted the disease to animals. Birley and Dudgeon (18) (1921) failed to transmit the disease from man to rabbits, and they regard such transmissions to animals as not proved. Gye (19) (1921) reports the results of the inoculation of 129 rabbits and 15 guinea-pigs with blood and cerebro-spinal fluid from 21 patients. None of the guinea-pigs showed any paralysis; 17 of the rabbits became ill and paralysed and 112 remained in good health. Of the 21 sets of experiments in which rabbits were injected 12 were completely negative. He concluded that disseminated sclerosis is an infective disease, and that the virus may sometimes be found in the cerebro-spinal fluid. Pettit (20) (1922) studied four cases of the disease, and from the spinal fluid of each it was possible to infect either monkeys, guinea-pigs, or rabbits. He passed the disease from a monkey through five rabbits in succession.

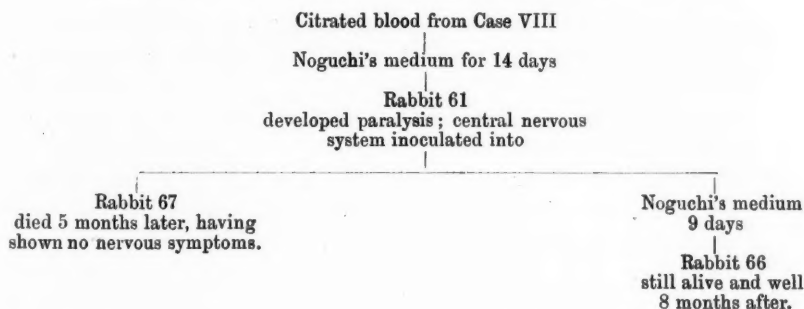
In the present investigation the inoculation of cerebro-spinal fluid into rabbits from nine cases of disseminated sclerosis produced nervous symptoms in five animals out of sixteen, and of the nine cases five yielded positive results. Of the animals showing nervous signs three (R. 5, R. 10, R. 55) showed paralysis of their legs, while two (R. 13, R. 27) showed typical cerebellar symptoms. On using citrated blood for inoculation from eight cases of the disease, nervous symptoms were noted in five out of eleven animals, three (R. 16, R. 18, R. 23) showing permanent paralysis of their legs, one (R. 17) showing transitory paralysis

of its legs of a month's duration (Plate 12, Fig. 1), and the remaining one (R. 28) showing typical cerebellar symptoms. Of the eight cases three yielded positive results.

When emulsions of the central nervous system of rabbits showing paralysis were used for inoculation, nervous symptoms were obtained in two rabbits out of eleven. In the one case the emulsion was glycerinated and had stood at room temperature for forty-eight hours after being prepared, and the animal (R. 9) which received this showed permanent paralysis of one of its hind legs. In the other case the emulsion was made in saline and injected immediately, and the animal (R. 26) developed cerebellar symptoms (Fig. 2). In one instance a culture was employed; this was made as follows: Pieces of the central nervous system, including the cerebellum from one animal (R. 27, which showed cerebellar symptoms), were excised aseptically after the animal had been killed, and were sown in tubes of Noguchi's medium which were then incubated for fourteen days; 10 c.c. of the pooled cultures were injected intraperitoneally and 2 c.c. subdurally into a rabbit (R. 53) which developed paralysis ninety-nine days later. The course of the experiment is shown diagrammatically as follows:



Blood cultures. In one case citrated blood obtained from a patient (Case VIII) suffering from disseminated sclerosis was inoculated into tubes of Noguchi's medium, and the resulting cultures, after 14 days' incubation, were injected intraperitoneally into an animal (R. 61) which developed paralysis of the left hind leg 42 days later. The cultures, when examined by the usual methods (dark-ground illumination, &c.), showed no evidence of the presence of spirochaetes, but in the brain, liver, and suprarenal of the inoculated animal spirochaete-like structures were found both on dark-ground examination and in stained films. Attempts to culture these spirochaetes failed, and the rabbit (R. 66) which was inoculated with these negative cultures is still alive. The course of the experiment is diagrammatically represented as follows:



From these results it will be noted that nervous symptoms have been produced on inoculation of the various materials mentioned above in 14 out of 42 inoculated animals, 2 of the animals being still alive and well 8 and 9 months after inoculation. Material from 7 of the 10 cases yielded positive results. The disease appears capable of being passed from one animal to another (further passage has been attempted only on a small scale and so far without success), and also from one animal through culture to another. Observations on the last point, however, are too scanty to enable one to say whether the culture represents actually an enrichment of the virus owing to growth, or whether the positive results were merely due to persistence of the living organism.

The period before the nervous signs showed themselves in the inoculated rabbits varied from 8 (R. 5) to 197 days (R. 13).

The material was inoculated subdurally, intraperitoneally, or intratesticularly, and some animals received injections by two of these routes. The following table shows the relationship between the routes of inoculation and the positive results:

Route.	No. of Inoculations.	Nervous Symptoms developed in
Intraperitoneal	32	10
Subdural	1	—
Subdural and intraperitoneal	6	2
Intraperitoneal and intratesticular	3	2

The cerebro-spinal fluid and blood were inoculated in some cases immediately, and in others a few hours after withdrawal from the patient.

Microscopic examination—pathological changes. In the animals which developed nervous symptoms round-celled infiltration was found under the ependyma of the ventricles or in the cortex in four (R. 5, 16, 26, and 28, Plate 13, Fig. 3) out of the 14 animals showing nervous signs, while in two others (R. 1, R. 7) which had been inoculated, but had shown no nervous symptoms, similar changes were noted. Definite small haemorrhages were found in the central nervous system of two rabbits which had been inoculated with cerebro-spinal fluid, but had shown no nervous signs. In one case (R. 56) the haemorrhage, which was situated in the cortex cerebri, was accompanied by local round-celled infiltration (Fig. 4); in the other (R. 15), in which the cord was affected, no such cellular infiltration was noted. Degenerative changes were found in the myelin sheaths of the axis

cylinders of the central nervous system in one animal (R. 9), which survived for over a year after the onset of paralysis, out of 14 rabbits showing nervous symptoms. These histological changes were also looked for in 10 normal rabbits, but were never found, as well as in 15 rabbits inoculated with various bacteria or protein substances (Figs. 5 and 6).

Bacteriological observations. Spirochaete-like structures were seen in 7 out of 42 rabbits inoculated with material from cases of disseminated sclerosis. These structures showed fairly active movement of transition from one part of the field to another. They did not exhibit the quick vibratory movements of *Spirochaeta pallida*, and were not so highly refractile. They were coarser and thicker than that organism, showed 5 to 9 irregular spirals, and varied from 8 to 15 μ in length (Figs. 7 and 8). On account of their scanty numbers, their staining reactions have not been fully worked out, but they stained well by Fontana's method and by Becker's carbol-fuchsin method. Five (R. 5, R. 13, R. 26, R. 61, R. 55) of these 7 animals had shown nervous symptoms; the other 2 died one (R. 24) four months and the other (R. 56) three weeks after inoculation. All attempts to culture these spirochaetes in Noguchi's medium have failed. Attempts made to culture them in collodion sacs containing rabbit serum which were implanted intraperitoneally into rabbits also failed. In one case (Case VIII) citrated blood from a patient suffering from the disease was inoculated into Noguchi's medium, and although films from the medium examined by dark ground 7, 10, and 14 days later showed no spirochaetes, yet the animal (R. 62) into which these cultures were inoculated developed paralysis, and spirochaetes were found in its tissues (Fig. 8).

From a consideration of the above experiments it will be observed that when blood and cerebro-spinal fluid from cases of disseminated sclerosis were injected directly into rabbits by various routes, over one-third (10 out of 27) of the animals inoculated developed nervous symptoms, which appeared after very variable incubation periods (8 days to 197 days). Normal blood, cerebro-spinal fluid, and blood and cerebro-spinal fluid from other diseases have not produced paralysis or other nervous symptoms in seven animals so inoculated. Spontaneous paralysis has never been observed in about 200 rabbits housed in the laboratory during the course of the present research, and many of these animals were kept for periods of from four months to over a year. Further, repeated intraperitoneal injections into eight rabbits of various killed bacteria or of protein substances such as milk and foreign sera have not produced nervous signs in the animals receiving such injections.

The infective agent appears to be present in the blood and spinal fluid of the patients. The virus is capable of existing in the central nervous system of inoculated animals, as such material proved to be infective not only by direct inoculation but also after culture. The presence of spirochaetes has been noted in some of the inoculated animals. As regards the assignment of a causal relationship to these organisms it is not possible at present to make any definite statement. It is possible that they may be of the nature of an accidentally

associated infection. The fact that they were not found in infective cultures does not necessarily exclude them from the aetiological rôle, since the virus may be extremely scanty or may undergo alterations in its microscopic characters. The organisms here described do not closely resemble *Spirochaeta cuniculi* (21) found in superficial ulcerative processes in rabbits; also it is generally concluded that the latter do not invade the internal organs. The histological changes characterized by round-celled accumulations suggest a chronic infective or toxic lesion. The subependymal infiltration of round cells may be the result of the virus existing in the ventricular fluid, though this point was not investigated in the present series. Degenerative changes in the myelin sheaths were found only in one animal (R. 9). It is to be noted, however, that this animal had lived for over a year after the onset of the paralysis, which had persisted throughout. These changes were also looked for in the other animals showing nervous symptoms, but in them the symptoms had only been present for from a few days to four weeks. As regards the small haemorrhages found in certain cases it may be said that a traumatic cause can be practically excluded; accordingly it would appear that they may be of toxic origin. There is an absence of the chronic lesions so characteristic of the changes in the central nervous system in human cases of disseminated sclerosis, but it must be noted that human material is in general derived from cases of some years' standing. Observations in comparative pathology illustrate amply the fact that the same known infective agent may produce different grades of pathological change in animals of different species, an instance in point being the effects of tuberculous infection in man, cattle, and mice. Examination of the finer cytological changes in the nervous system has not been attempted in the present series. It may be stated definitely that degenerative changes in the central nervous system, which would account for the clinical signs, have been found in a proportion of the animals.

Further investigations are being carried out, especially as regards the culture of the virus and methods of enriching it and of enhancing its virulence. It is possible that the difficulties in the present case are similar to those which were met with in yellow fever: thus Noguchi found that in order to effect the demonstration of the causal organism it was necessary to enrich the virus by culture, then to inoculate susceptible animals, and further to effect passage at a suitable stage of the infection.

Treatment.

The treatment of disseminated sclerosis by means of salvarsan was first suggested by Buzzard (11) (1911); Kalberlah (23) (1919) reports the results of the treatment of numerous cases with sodium-silver-salvarsan. In early cases both sensory and motor symptoms showed marked improvement, but long-standing cases were unaffected. He concludes by suggesting that if ultimately disseminated sclerosis prove to be a spirillosis, sodium-silver-salvarsan may be expected to be as specific for it as salvarsan is for syphilis. A portion of our results relating

to 22 cases has already been published (1921) (24). Perdrau and Stebbing (5) (1921) record a case in which a diagnosis of combined sclerosis was made, the Wassermann reaction of the blood serum being positive, although there was no personal or family history of syphilitic infection. On admission to hospital the patient was bedridden. Intravenous injections of galyol were followed by dramatic improvement; subsequently septic infection of the urinary tract led to death, and post-mortem examination showed typical microscopical and macroscopical changes of disseminated sclerosis. They suggest that the intravenous injections of arsenic may have played some part in the striking clinical improvement which resulted. Byrnes (9) (1922) reports the results of the treatment of five cases of the disease with arsphenamin; all the cases showed some improvement, but he is inclined to attribute this to the possibility of syphilis being an aetiological factor.

In estimating the effects of any remedial agent in disseminated sclerosis, great difficulty arises on account of the spontaneous remissions which occur in the normal progress of the disease. This difficulty should not, however, prove insuperable, though obviously prolonged observation is necessary before any conclusions are justifiable. Charcot regarded this tendency to remission as a definitely favourable factor in disseminated sclerosis. In this connexion he stated: 'The prognosis has hitherto been of the gloomiest. Shall it be always thus? It is to be hoped that when the disease has become better known the physician will learn how to take advantage of that spontaneous tendency to remission which has been noted in a great number of cases.' He also states with great clearness the second of the difficulties which beset the therapy of disseminated sclerosis: 'The real nature of the disease is not recognized until the lesions have become well marked and are consequently but little amenable to the influence of therapeutic agencies.'

During the progress of the present research we have been increasingly impressed with this necessity for early diagnosis, i.e. a recognition of the disease at the stage in which symptoms of disordered functions are present, but in which signs of permanent and irreparable damage have not yet developed. The importance of the correlation of such symptomatology of onset with a positive reaction to colloidal gold has been emphasized here and elsewhere. The adoption of a purely negative attitude towards the disease, which rejects the possibility of accurate diagnosis until the condition is obvious (and incurable), and which attributes in advance any improvement under treatment to a natural remission, will leave disseminated sclerosis in its present position of an incurable and fatal disease. It is of great interest to note that Marie, in his lectures in 1891 (10), formulates the definite opinion that in disseminated sclerosis there are two factors, the one 'sclerotic', the other 'infective'. For the first factor he recommends potassium iodide, for the second he urges the long-continued use of mercury. 'It must be well understood', he writes, 'that this medicine is not given as an anti-syphilitic, since syphilis appears to play but the slightest or no part in the aetiology of true insular sclerosis. It is only on account of its disinfecting pro-

perties that I would recommend its administration.' Marie thus adopts the attitude that although disseminated sclerosis is not syphilitic in origin, it should be treated on antisyphilitic lines. In 1911 Buzzard (11), in a most interesting contribution to the literature, advocated the prolonged exhibition of mercury and arsenic, although he hesitated to draw definite conclusions from the cases he had so treated. In this article he suspected the existence of some organism allied to *Spirochaeta pallida*, and this is the first suggestion of a causal spirochaete that we have been able to trace in the literature of the disease. In the light of Ehrlich's then recent discovery he advocated the future use of salvarsan 'as soon as the experimental stage in its employment has been completed'. No results of such treatment have, however, been so far published by him. The employment of arsenic is also recommended by Risien Russell (25), Bramwell (26), and Osler (27). In view of the weight of evidence that arsenic, mercury, and iodide appear to have some therapeutic value, it is logical to consider the administration of arsenic in its most efficient form as a salvarsan compound, especially as this disease is under considerable suspicion of being spirochaetal in origin.

Treatment employed in the present research. The treatment which has been carried out in the cases under review is as follows: The patient receives a preliminary course of 10 days' mercurial inunction combined with the oral administration of potassium iodide. 0.3 grm. novarsenobillon is then given intravenously, and if no reaction is noted the dosage is increased to 0.45 grm. Three initial courses of four injections each are given, the administration of mercury and iodide being carried on at the same time. The patient is then given arsenic by the mouth for several months, after which a second series of salvarsan injections is administered. Intermittent treatment on these lines is continued over a minimum period of two years.

In estimating the results obtained in any individual case the first question to consider is, in how far is recovery possible? i. e. how much permanent damage has already been done? Highly specialized nervous tissue has minimal recuperative power. No therapeutic agent can be expected to regenerate a destroyed myelin sheath or remove a patch of sclerosis which is to all intents and purposes scar tissue. On the other hand, the earlier pathological changes, e.g. round-celled infiltration acting either by direct pressure on adjacent nervous structures or by interfering with the blood supply, may possibly be removed.

Secondly, it must be emphasized that in a disease which normally runs a progressive downward course any remedy which tends to arrest this progress at the stage at which the disease is first encountered is extremely valuable and should not be withheld, because it cannot confer upon a tissue regenerative powers which it does not possess. It is, therefore, a logical conclusion that no remedy can ever be expected to 'cure' advanced cases of this disease when the whole nervous system is riddled with plaques of sclerosis. The supreme object of treatment must be towards eradication of the infective agent in the earliest stages of the disease, and thus the necessity for early diagnosis cannot be over-emphasized.

The present series of cases includes those submitted to treatment both in the early and later stages. As regards the early cases, remarkable improvement has been frequently observed. It is to be noted that in some instances the diagnosis could not be dogmatically established in the sense that all the cardinal signs were not present; the occurrence of a paretic or luetic reaction of the cerebro-spinal fluid with colloidal gold and a negative Wassermann reaction has left little doubt in our minds that these cases were in reality genuine disseminated sclerosis. If they do not belong to this category, the difficult problem presents itself as to what serious disease of the central nervous system they represent. Further, the question of spontaneous remissions has seriously to be entertained; also the lapse of time has been insufficient to warrant the conclusion that permanent arrest of progress has been effected. As regards the later cases, persistent treatment has resulted in improvement, which has almost constantly occurred, and so far there has not been subsequent deterioration. Consequently it would appear that the process of progressive degeneration has been brought to a standstill, although, as has been stated already, it was not possible to restore function performed by tissue already destroyed.

Control observations on cases of neurosyphilis of approximately the same stage of development have been carried out, and we are distinctly of the opinion that the cases of disseminated sclerosis have shown more constant and definite improvement than cases of neurosyphilis presenting a similar grade of severity of symptoms. Examples of selected cases are shown in the appendix.

Conclusions.

The prospects of satisfactory treatment of disseminated sclerosis depend upon early diagnosis; therefore it is essential to recognize the disease before irreparable damage of nervous tissue has occurred, i. e. before the development of the 'cardinal' signs. Early manifestations are related especially to the 2nd, 3rd, and 6th cranial nerves, the bladder centre, and to certain subjective sensory phenomena.

Syphilis may produce practically identical phenomena. In both conditions the cerebro-spinal fluid shows a positive colloidal gold reaction. Emphasis is laid on the fact that one group of cases reacts negatively to the Wassermann reaction both with blood and cerebro-spinal fluid, and presents no other evidence of syphilis. Cases giving a positive Wassermann reaction are excluded from the category of disseminated sclerosis in the present paper.

In confirmation and extension of experimental work of others, it has been shown that nervous phenomena (paralysis of limbs and cerebellar symptoms) develop in animals which have received injections of blood or cerebro-spinal fluid from cases of disseminated sclerosis. Passage of the condition to a second animal has been successful in several instances. Positive inoculation results have been obtained with material both from cases and from experimental animals after transmission through culture. The symptoms in animals have developed in about 30 per cent. of those inoculated, after very variable latent periods.

Spirochaete-like organisms have been found in a proportion of inoculated animals in various internal organs. These spirochaetes have been seen both in animals affected with as well as in some free from nervous symptoms. Cultivation of the spirochaetes has not succeeded, and at present their causal relationship to the disease is undecided.

The treatment of cases of disseminated sclerosis by drugs of the salvarsan class has given very promising results, which exceed those obtained by similar treatment in cases of neurosyphilis symptomatically similar.

We desire to express our indebtedness to Professor T. K. Monro for his help and for the extension of clinical facilities which he afforded us throughout; also to Dr. Brownlow Riddell and Dr. H. Wright Thomson for their assistance in connexion with the ocular manifestations of the disease.

APPENDIX.

In this appendix are included clinical summaries of cases used for inoculation purposes, and also a few additional selected cases in which treatment has been carried out. For the sake of brevity negative clinical findings have not generally been included.

Case I. (Index No. 142.) Male, aged 39, clerk.

History of onset. In 1899, following upon a severe chill, he noticed numbness and tingling of his legs. This was followed by a weakness of the right side of the face, the right arm, and the right leg, which spontaneously recovered in seven weeks. He remained well for approximately a year, when the weakness of the right side returned, and soon after this he first noted diplopia. His condition steadily deteriorated until 1918, when he became unable to walk and was confined to bed for several months. In 1919 tremor of his arms became marked and difficulty in speaking was noted.

Condition on admission, 1.10.20. He walked with great difficulty and with the help of two sticks, the gait being of the scissors type. The pupils were equal and reacted normally: coarse lateral nystagmus was present: examination of the fundi revealed bilateral optic atrophy. There was gross intention tremor and the speech was definitely staccato. The arm reflexes were all increased. The legs were weak and spastic, the knee-jerks were increased and ankle and patellar clonus were present on both sides. The plantar reflexes were strongly extensor.

W.R. blood negative. Cerebro-spinal fluid, W.R. negative. Cell count 3 per c.mm.: no excess of protein. Colloidal gold reaction 11221000000.

Comment. This case presented all the cardinal signs of disseminated sclerosis.

Case II. (Index No. 172.) Female, aged 29, piano teacher.

History of onset. In the spring of 1918 the patient noticed that she tended to drag the right leg; some months later she suffered from trembling of the hands and inability to convey a cup to her lips without spilling the contents. Her speech began to change about April 1918, becoming definitely slower. In October 1919 she had to abandon her occupation, and involuntary shaking of the head of intermittent incidence became evident.

Previous health. Beyond an attack of measles in childhood, and recurrent attacks of tonsillitis during adolescence, she suffered from no acute infection.

Family history. This contained no fact of note.

Condition on admission. The head moved in a regular fashion from side to side about 100 times to the minute (this a few hours later was seen to have stopped entirely). The extended hands showed a coarse, irregular tremor; intention tremor was present, more marked on the right side. The pupils were equal and reacted normally to light and on accommodation: coarse nystagmus was present: both fundi were normal. No history of diplopia was obtained. The abdominal reflexes were absent. The left knee-jerk was normal, the right exaggerated. Both plantar reflexes gave an extensor response. Sustained ankle clonus and slight patellar clonus were present on right side, none on left. The speech was slow, deliberate, and definitely of the staccato type. Incontinence of faeces was present.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative? Cell count 3 per c.mm.: no excess of protein. Colloidal gold reaction 55552100000.

Treatment. Patient received three months' treatment with mercury and iodide, and, concurrently, twelve injections of 0.45 grm. novarsenobillon.

Result. Her general condition showed material improvement. The tremors of the hands and head diminished, nystagmus became less marked, and the speech definitely improved. The colloidal gold reaction was again examined at the conclusion of treatment (19.1.21) and gave a negative result. She was discharged at the end of January 1921 and no further treatment was carried out until six months later, when she had a slight relapse and further salvarsan therapy (12 injections in all) was carried out by her own doctor, who reported almost immediate improvement in her condition. On 31.12.22 she was still unable to walk unaided, but her intention tremor had sufficiently diminished to enable her to feed herself with a fork and to play the piano for over an hour. The opinion of herself, her own medical attendant, and her relatives was that she was gradually and steadily improving.

Comment. The combination of spastic paraplegia, absent abdominal reflexes, nystagmus, intention tremor, and scanning speech with a paretic gold curve and a negative Wassermann reaction in a woman of 29 justifies the diagnosis of disseminated sclerosis. Clinical improvement coincided with energetic anti-specific treatment. The colloidal gold curve changed from paretic to negative. A subsequent relapse was controlled by further administration of salvarsan, the patient in the interval having had no treatment. Further observation is of course necessary before drawing any very definite conclusions.

Case III. (Index No. 30.) Male, aged 22, apprentice plater.

History of onset. In November 1917, following upon an attack of trench fever, he complained of numbness of the feet and difficulty in walking. Since then the weakness of his legs had gradually increased. There was no history of injury or of venereal infection.

Family history. Negative.

Condition on admission, 11.11.20. The patient was unable to stand and had complete incontinence of urine and faeces. The pupils were moderately dilated and reacted directly and consensually to light and on convergence. There was well-marked lateral nystagmus. Both optic disks were pale and parchment-like, the cribriform plate being very distinctly seen. The left eye was worse than the right. Coarse intention tremor was present, more marked on the left side. The abdominal reflexes were absent: the knee-jerks were both increased: sustained ankle clonus was present on both sides: the plantar reflexes were extensor. Speech was typically scanning.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative. Cell count 2 per c.mm.: no excess of protein. Colloidal gold reaction 555422000.

Treatment. From 11.11.20 to 15.3.21 patient was treated with mercury, iodide of potassium, and weekly injections of novarsenobillon. Minor improvement was noted in respect of diminution of tremor and almost complete regain of bladder function. His condition otherwise remained unaltered.

Case IV. (Index No. 194.) Male, aged 32.

History of onset. He first noticed weakness of the legs in January 1916. His condition steadily deteriorated and in the summer of 1918 he became rapidly worse: diplopia, incontinence of urine, tremors, and change in speech all developing with rapidity.

Previous health. Good. No history of venereal infection.

Family history. Negative.

Condition on admission. He was unable to stand. The pupils were equal and reacted to light, directly and consensually, and on accommodation. Slight lateral nystagmus was present. There was paresis of left internal rectus muscle with diplopia. The visual acuity was good. Both fundi were normal. Slight intention tremor was present. The abdominal reflexes were absent. The knee-jerks were increased. Sustained ankle clonus was present on the right side. The plantar reflexes were strongly extensor. There was frequency and partial incontinence of urine. The speech was markedly staccato.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative; fluid slightly contaminated with blood. Colloidal gold reaction 12321000000.

Treatment. From 7.1.21 to 10.5.21 he was treated with mercury, iodide, and intramine, and also received ten injections of 0.45 grm. novarsenobillon.

Result. His general condition improved, tremors became less marked, and he regained his ability to write. Sphincter control was partially recovered. Otherwise his condition remained unaltered.

Case V. (Index No. 212.) Male, aged 27, plumber.

History of onset. In July 1916 he sustained a severe fall and a slight wound in the leg. In June 1917 he complained of shakiness and unsteadiness in walking. His condition was diagnosed as functional. During 1918 the weakness of his legs increased, and by September 1919 he was unable to stand. He had since been resident in various hospitals.

Previous health. He had an attack of scarlet fever in 1910 and in 1918 he suffered from influenza. There was no history of venereal infection.

Family history. This contained no information of note.

Condition on admission, 19.1.21. The patient was well nourished and of good physique. He was unable to stand. The pupils were equal and reacted directly and consensually to light and on convergence. There was slight nystagmus: diplopia was present. The visual acuity was R. 6-18, L. 6-36. The fields of vision were uncontracted, but there was a central scotoma for all colours. The optic disks were both white and had exudate on them indicating past optic neuritis. There was very coarse intention tremor of both arms. The abdominal reflexes were absent. The knee-jerks were both increased. Ankle clonus was obtainable on both sides. The plantar reflexes were strongly extensor. There was marked spasticity and loss of power of the legs, and the patient was unable to extend the legs. The speech was definitely slower than normal. There was absolute incontinence of urine and faeces.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative; fluid contaminated with blood.

Case VI. (Index No. 1.) Female, aged 18.

History of onset. Two weeks prior to admission, and following upon an attack of subacute rheumatism, she began to complain of numbness of the right side of her body.

Family history. Contained no fact of note.

Condition on admission, 3.8.19. General nutrition was good. The right pupil was slightly smaller than the left: both reacted to light and on accommodation. Movement of the right eyeball caused pain. There was no nystagmus. The right optic disk was swollen, the upper part of the margin being lost and the veins unduly full. There was no intention tremor. The abdominal reflexes were absent. The knee-jerks were both increased. The plantar reflexes were doubtful. The arm reflexes were over-active on the right side. There was no loss of sensation in any part of the body, but it was slightly defective in the right arm and leg as compared with the left. On 5.9.19 the right plantar reflex was definitely extensor.

Cerebro-spinal fluid, W.R. negative. Cell count 2 per c.mm.: no excess of protein. Colloidal gold reaction 11222100000.

She was discharged from hospital and readmitted on 26.1.20 complaining of loss of power of the left arm. Fine lateral nystagmus had developed in both eyes, and definite pallor of the right disk was noted. The plantar reflexes were both extensor. Slight impairment of vibration sense was detected in the left leg.

Case VII. (Index No. 231.) Male, aged 24, coal miner.

History of onset. His illness originated shortly after he was blown up by a mine in 1916, when he complained of weakness and tremors, the condition being regarded as functional. In November 1918 he complained of diplopia and frequency and precipitancy of micturition.

Family history. Negative.

Condition on admission, 5.4.21. His general condition was good. He was somewhat neurasthenic. The pupils were equal and reacted to light, directly and consensually, and on convergence. There was slight lateral nystagmus. Coarse intention tremor was present, more marked on the right side. The abdominal reflexes were present, but were sluggish and easily exhausted. The knee-jerks were increased. Patellar clonus and ankle clonus were elicited on right side, but not on left side. The plantar reflexes were both strongly extensor. The legs were weak and markedly spastic. Frequency and precipitancy of micturition were present. There was anaesthesia over outer aspect of left leg. No other sensory abnormality was noted.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative. Cell count 4 per c.mm.: no excess of protein. Colloidal gold reaction 22232000000.

Treatment. From 5.4.21 to 21.6.21 the patient was treated with mercury and potassium iodide and received concurrently 11 injections of 0.45 gm. novarsenobillon.

Result. Regain of bladder control and slight improvement in general condition were noted on discharge.

Case VIII. (Index No. 268.) Male, aged 25, clerk.

History of onset. In September 1917 he complained of weakness and dragging of left leg, headaches, and diplopia. The condition was regarded as functional. He remained in hospital for 12 months, and during this period his condition varied from time to time. In July 1921 his symptoms became worse and he complained of frequency of micturition; a few months later he was troubled with occasional incontinence of faeces. In December 1921 he complained of weakness in the right leg, and in January 1922 he had sudden and almost complete loss of power in both legs.

Previous health. Patient was always nervous and highly strung. No serious illnesses were recorded: there was no history of trauma.

Family history. Contained nothing of note.

Condition on admission. The legs were weak and spastic. The knee-jerks were both exaggerated. Ankle clonus was elicited on both sides. The right plantar reflex was extensor, the left indefinite. The abdominal reflexes were

absent. There was no true intention tremor, but definite incoordination of the arms. There was marked weakness of grip with the left hand. Frequency and precipitancy of bladder and bowels were present. The speech was slurring in character. The pupils reacted to light and on accommodation. Nystagmus was not present.

From 23.9.21 to 10.3.22 the Wassermann reaction was examined on six occasions with negative result. Cerebro-spinal fluid, W. R. negative. No excess of protein. Colloidal gold reaction 33344210000.

Treatment. For three months patient was treated with mercurial inunction and potassium iodide. During this period he received 12 injections of novarsenobillon varying from 0.3 to 0.6 gm. per dose.

Result. His condition materially improved. Muscular power was almost completely regained in his legs and his gait was practically normal. Definite improvement was also noted in his speech. He was discharged 14.3.22 and returned to his work, which he had since steadily followed.

Salvarsan treatment was recommended 14.11.22, since when he had had a further course of six injections. He stated that the muscle power of his legs was steadily improving. Mental condition markedly neurasthenic. Knee-jerks both moderately exaggerated. Both plantar reflexes flexor.

Comment. The combination of spastic paraplegia, diplopia, paraesthesiae, and temporary uselessness of an arm occurring in a young adult with a repeatedly negative Wassermann reaction justifies the diagnosis of disseminated sclerosis. The disease in this case was not advanced, and consequently in estimating the results of treatment it is not possible definitely to exclude spontaneous remission. It is noteworthy that the remission coincided with treatment and has been maintained for a period of eleven months.

Case IX. (Index No. 282.) Male, aged 29, purser.

History of onset. Following upon a severe fall in the spring of 1918 he complained of increasing weakness and stiffness of right leg. Shortly prior to admission the left leg became involved.

Condition on admission, 11.10.21. The general condition was good. X-ray examination of spine showed no abnormality. There was marked loss of power in the right leg and slight loss of power in the left. The knee-jerks were increased and patellar clonus could be elicited. Both plantar reflexes were extensor. The abdominal reflexes were absent. Tactile and pain sensation were diminished in the upper part of the right thigh and there was hyperaesthesia below the knee on the outer aspect of the right leg. The pupils were equal and reacted normally: there was no nystagmus. The fields of vision were not contracted. There was definite pallor of both optic disks, but no central colour scotoma. Ataxia of arms was present, but typical intention tremor had not developed. There was frequency and precipitancy of micturition. Bowel function was normal. Occasional impediment of speech was noted, but typical staccato speech was not present.

W. R. blood negative. Cerebro-spinal fluid, W. R. negative. Cell count 2 per c.mm.: no excess of protein. Colloidal gold reaction 32222100000.

Comment. This case did not present a fully-established clinical picture of disseminated sclerosis. The diagnosis was based on bilateral pyramidal involvement with extensor plantar responses, absence of the abdominal reflexes, pallor of optic disks, and derangement of bladder function.

Case X. (Index No. 352.) Male, aged 26, engineer.

History of onset. The patient was torpedoed 1.1.17, being blown up and stunned; he was lifted into a lifeboat which sank under him and he was flung into the sea; he kept afloat with the aid of a life-belt and was picked up after one hour. He was admitted to hospital, where he remained for 3½ months.

On leaving hospital he complained of weakness and dragging of left leg. In December 1917 he contracted malaria and dysentery. In 1918 he suddenly collapsed at his work and was laid up for some months. At this period he also complained of diplopia. Early in 1921 his legs became so weak he was unable to walk, and later in the same year gross tremor of the hands developed. In March 1922 slowness of speech was noted.

Condition on admission, 10.3.22. Patient was bedridden and had complete incontinence of urine and faeces. His mental condition was euphoric; general nutrition was fair. There was constant nystagmus in every direction. The pupils were equal and reacted actively to light and on accommodation. There was marked temporal pallor of both optic disks; detailed examination was difficult on account of nystagmus, but there appeared to be a central defect for colours, i.e. there seemed to be a partial optic atrophy in both eyes. Gross intention tremor of both arms was present. Speech was slow, monotonous, and scanning. The knee-jerks were both exaggerated. The left plantar reflex gave a doubtful extensor response, the right was flexor. The abdominal reflexes were absent. No abnormality of tactile or temperature sense was detected. Pain sense and muscle-joint sense were slightly defective in legs.

Wassermann reaction of blood negative. Cerebro-spinal fluid, W.R. negative. Cell count 4 per c.mm.: no excess of protein. Colloidal gold reaction 43321000000.

Treatment. Continuous administration of iodide combined with mercurial inunction. During the period March 1922–December 1922, twenty-six injections of novarsenobillon were given in intermittent courses.

Result. He regained bladder control; bowel control which on admission was lost was partially regained. His general condition was steadier. Nystagmus was definitely less marked.

Comment. Evidence of gross permanent damage was present in this case at commencement of treatment. His condition did not deteriorate and minor improvement was obtained. The regain of sphincter control has ameliorated his condition and minimized the risk of death from septic absorption.

Case XI. (Index No. 14.) Male, aged 24, miner.

History of onset. The onset of his symptoms dated from March 1919. His previous health had been good. He contracted jaundice at Gallipoli in November 1915, and about the same period suffered from dysenteric infection.

Condition on admission, 12.12.19. A well-developed, well-nourished man of healthy appearance. The pupils were equal, reacted actively to light, directly and consensually, and on convergence. Lateral nystagmus was present. The left optic disk was distinctly pale, the right showed some congestion of the vessels. There was a past history of diplopia. Legs were spastic, the knee-jerks were exaggerated. The left plantar reflex was extensor, the right flexor. There was marked incoordination of arms, but no true intention tremor. The abdominal reflexes were absent. Hesitancy and slight retention of micturition was present. He complained of numbness and tingling of legs and of right hand.

Serological findings. W.R. blood negative. Cerebro-spinal fluid, W.R. negative; fluid faintly contaminated with blood. Colloidal gold reaction 55553210000.

Treatment. During the period December 1919 to June 1920 the patient was treated with intermittent courses of mercurial inunction and oral administration of potassium iodide. In addition he received ten injections of novarsenobillon.

Clinical result of treatment. His general condition showed definite improvement and he no longer complained of attacks of giddiness. Slight improvement in muscle power of legs and of gait was noted. The plantar responses remained extensor. He was discharged 11.3.20. His condition

remained stationary until June 1922, when the condition of his legs became slightly worse. He was readmitted on 9.9.22, when his condition was objectively unaltered since his discharge. Antispecific treatment was recommenced and combined with re-education exercises and massage. Under these he is showing some improvement in gait. His bladder symptoms are unaltered—diplopia is not complained of.

Comment. Arrest of progress in this case coincided with the first administration of antispecific treatment. A minor relapse was immediately checked by further salvarsan administration. The man is positive in his statement that he has materially benefited from the treatment he has received.

Spontaneous arrest cannot of course be definitely excluded and a further prolonged period of observation is necessary before definite conclusions can be drawn.

Case XII. (Index No. 380.) Female, aged 24, nurse.

Onset of present illness. In May 1922 she complained of severe pain in right flank and thigh which persisted for three weeks. On June 12 she complained of numbness in right thigh and noted that the affected limb was stiff and weak.

Previous health. Measles in infancy. Diphtheria three years ago.

Family history. Negative.

Condition on admission, 30.6.22. Patient was unable to stand. The knee-jerks were both increased, the right being more definitely exaggerated than the left. The right plantar reflex was extensor, the left absent; ankle and patellar clonus present on right side, absent on left. The abdominal reflexes were absent on both sides. Organic reflexes were normal. There was loss of perception of light touch on the plantar surface of all the toes of the right foot and over the ball of the foot. Over the same area there was confusion of differentiation between sharp and blunt. There was very slight intention tremor in right hand. The pupils were equal and reacted normally. There was no nystagmus or diplopia. The fundi were normal.

W.R. blood negative. Cerebro-spinal fluid, W.R. negative. Cell count 3 per c.mm.: no excess of protein. Colloidal gold reaction reaction 112321000.

Treatment. Patient was treated with mercurial inunction and potassium iodide, gr. xv. t.i.d., from 1.8.22 to 2.10.22. She received thirteen injections of 0.3-0.45 gm. novarsenobillon intravenously.

Clinical results of treatment. Uninterrupted improvement took place. Numbness and pain in the affected limb disappeared, and muscular power in large measure returned. She was discharged from hospital after a residence of 3½ months. She was then able to stand and walk unaided and the right plantar reflex was definitely flexor on repeated examination. Since discharge her condition has further improved and she is now able to walk a considerable distance without help.

Comment. The combination of a spastic monoplegia, paraesthesiae, and intention tremor occurring in a woman of 24 years with a negative Wassermann reaction indicates a probable diagnosis of disseminated sclerosis. The remission of symptoms was almost complete and coincided with treatment.

Case XIII. Male, aged 20.

History of onset. In February 1919, following upon an attack of influenza, he complained of shakiness of hands and unsteadiness of gait; about the same time he suffered from blurring and dimness of vision. By the summer of 1919 he had become unable to walk and was confined to bed. In November 1920 his condition became markedly worse and he commenced to lose weight. His previous health had been good, but he was always 'highly strung' as a child.

Condition on admission, 1.3.21. Patient was in a debilitated and helpless condition and had a toxic appearance. Malnutrition was marked. When

propped up on pillows he tended to slide down into the bed. An almost constant tremor of the head was present. There was incontinence of urine and faeces, with the presence of a sacral bedsore. The urine contained a copious deposit of pus and when freshly passed was strongly acid.

The left pupil was smaller than the right: both pupils reacted to light, directly and consensually, and on convergence. Constant nystagmus was present. There was no central scotoma for white or colours, and no definite optic atrophy was detected. The legs were definitely spastic and showed great muscular weakness, the left being practically useless. The knee-jerks were both exaggerated, the left more than the right. Ankle clonus was present on both sides. The plantar reflexes were both extensor. The abdominal reflexes were absent. Gross intention tremor which prevented any co-ordinated movement of arms was present. Speech was slow, slurring, and almost unintelligible.

W.R. blood negative. W.R. of cerebro-spinal fluid negative.

This case presented a clinical picture of disseminated sclerosis almost in the terminal stage. Intensive treatment was adopted as follows: Mercurial ointment prepared according to the Aachen formula was rubbed in by a skilled masseur daily for 10 weeks, the dose being gradually reduced as salivation developed. Potassium iodide, gr. x. t.i.d., was administered in intermittent courses. Novarsenobillon, 0.3 grm., was given intravenously at 5-day intervals for 10 weeks. The patient also received repeated injections of 3 c.c. intramine. At the end of these 10 weeks of intensive treatment his condition had sufficiently improved to justify further endeavour. The muscular weakness and involuntary tremors were much less marked, nystagmus and intention tremor had diminished, bowel control had been regained, and the bedsore had healed. After two weeks' respite Donovan's solution was given orally for six weeks, and in July 1921 four further weeks of intensive salvarsan administration were carried out. The bladder control was still deficient and pyuria markedly present. Urotropin having produced no improvement, the urine was rendered alkaline and an autogenous vaccine was given. This was followed by regain of bladder control and complete disappearance of pus from the urine. The patient was discharged 1.8.21 with instructions to continue intermittent courses of liquor arsenicalis alternating with mercurial inunction. He was readmitted 1.10.21, when his condition was greatly improved. The toxic appearance of the skin had cleared up and bladder control was normal. Commencing 1.10.21, a further six weeks' course of salvarsan administration was given, after which a month's rest was ordered and then liquor arsenicalis and mercurial inunction were recommenced. During 1922 two four-week courses of salvarsan were given and, in the intervals, short courses of Donovan's solution were administered.

Present condition. Patient's health was greatly improved and he had markedly gained weight and muscular power. Bladder and bowel function had been normal for nine months and the urine contained no pus cells on centrifugalization. He could stand unaided for 60 seconds, and with a stick and the support of a nurse's arm could walk a distance of 200 yards. The intention tremor had sufficiently diminished to enable him to place a cigarette between his lips. Nystagmus was definitely less marked and the involuntary tremor of the head at rest had disappeared. The condition of the tendon reflexes remained unaltered.

Comment. This case presented four of the five cardinal signs of disseminated sclerosis; the age of the patient and history of onset precluded the possibility of a mistaken diagnosis. The case was encountered in what may fairly be described as the terminal stages of the disease. Steady and uninterrupted improvement in minor details accompanied the administration of antispasmodic treatment. The complete regain of sphincter control was striking. Further improvement is improbable on account of the extensive permanent damage that has presumably been done, but modified treatment is being continued with a view to preventing the occurrence of relapse.

Case XIV. (Index No. 221.) Male, aged 27, chauffeur.

History of onset. First noted a slight shakiness of fingers in August 1917. Later paraesthesiae of left arm developed, beginning with tingling of fingers. Still later he began to drag his left leg. About the beginning of 1922 he noticed a slight defect in vision of left eye and a tendency to fall to left. In April 1922 his condition was so bad he was unable to stand and diplopia and bladder symptoms began to trouble him.

Condition on admission, 29.6.22. Patient was bedridden and unable to stand. He was well nourished and the complexion was fresh; his mental condition was euphoric. Marked tremors of head were present. There was constant nystagmus: the pupils were equal, moderately dilated, and reacted actively to light and on accommodation. Paresis of right external rectus muscle was present. Central colour scotoma for green was present. There was marked pallor of both optic disks, especially in temporal halves. Abdominal reflexes were absent on both sides. The knee-jerks were increased. The plantar reflexes were both extensor. There was a gross intention tremor, especially marked on left side. The speech was slow and scanning. Hesitancy of micturition and slight retention of micturition were present. Bowel sphincters were normal.

W.R. blood negative. Cerebro-spinal fluid, W.R. negative. Cell count 0 per c.mm.: no excess of protein. Colloidal gold reaction 3333200000.

Gastric analysis. Free HCl absent. Tests for lactic and acetic acid negative.

Treatment. On admission mercurial inunction and the oral administration of potassium iodide in doses of gr. x. t.i.d. were commenced and have since been carried out more or less continuously. From 4.7.22 to 10.12.22 15 injections of novarsenobillon were given intravenously.

Antispecific treatment was also combined with orthopaedic treatment consisting of massage and re-education.

Result (10.12.22). Definite improvement in muscles of legs. Considerable return of muscular power: could stand with assistance and could walk 100 yards with a stick, a nurse taking his other hand. The head could usually be held steady without tremor. The intention tremor of the arms had diminished and he was able to button up his shirt-sleeves. He had completely regained bladder control and suffered from no urinary defect.

Comment. This case presented all the cardinal signs of established disseminated sclerosis. Progressive clinical improvement coincided with anti-specific treatment. He stated that previous residence in hospital, when no anti-specific treatment was given, produced no amelioration of symptoms.

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DESCRIPTION OF PLATES.

PLATE 12, FIG. 1. Photograph of Rabbit 17, fourteen days after the onset of paralysis in the hind legs, which are drawn after the animal.

FIG. 2. Three photographs of Rabbit 26 ten days after onset of cerebellar symptoms.

- A. The animal's head is rotated over to the left side, towards which it is rolling over.
- B. The animal falls over farther to the left side and tries to recover the upright position by pushing out its foreleg to the left.
- C. The animal has lost its balance and is just in the act of rolling over to the left.

PLATE 13, FIG. 3. Section of brain stained by haematoxylin and eosin of R. 28, showing infiltration under the ependyma of the lateral ventricles. The lining ependyma on one side has been stripped off during the preparation of the specimen ($\times 250$).

FIG. 4. Section of brain of R. 56 (stained by haematoxylin and eosin), showing haemorrhage in the white matter under the cortex, together with slight round-celled infiltration at places in and around the haemorrhage ($\times 80$).

FIG. 5. Section of lumbar portion of cord from R. 9 (stained by Marchi's method), showing some scattered degeneration of myelin sheaths, and also degeneration of the nerves emerging from the anterior horn ($\times 60$).

FIG. 6. Section of cord from lower dorsal region of R. 9 (stained by Marchi's method), showing degeneration in the myelin sheaths in the anterior tracts on both sides of anterior median fissure ($\times 60$).

FIG. 7. Film from liver of R. 24 (stained by Becker's carbol-fuchsin method), showing a spirochaete-like structure. The irregular coarse spirals are well seen ($\times 1,500$).

FIG. 8. Film from the liver of R. 61 (stained by Becker's method), showing a spirochaete-like structure with coarse irregular spirals ($\times 1,500$).



FIG. 1. Rabbit 17, showing paralysis of 14 days' duration.



FIG. 2 A. Rabbit 26, showing cerebellar symptoms of 10 days' duration.



FIG. 2 B. Same as 2 A; animal falling over farther to left side.



FIG. 2 C. Same as 2 A; animal lost its balance and falling over.

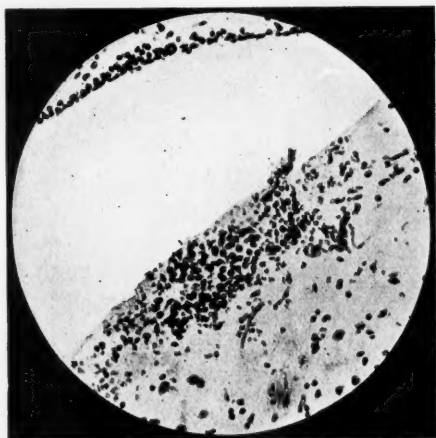


FIG. 3. Section of brain; subependymal infiltration.

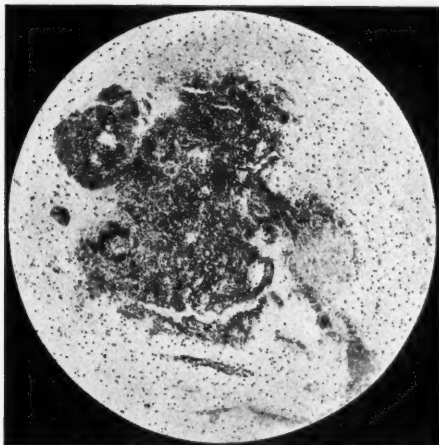


FIG. 4. Section of brain; haemorrhage in white matter.

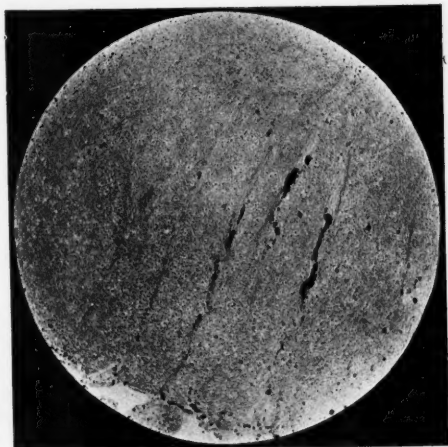


FIG. 5. Section of cord; degeneration of motor nerves and myelin sheaths (Marchi).

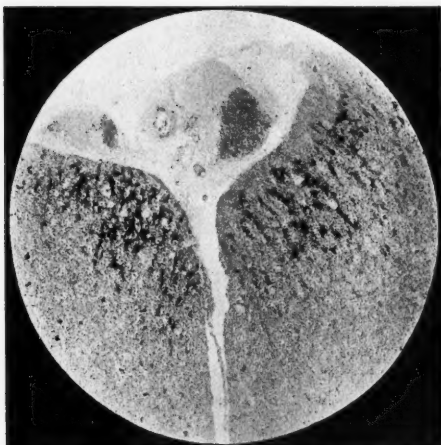


FIG. 6. Section of cord; degeneration of myelin sheaths in anterior columns (Marchi).

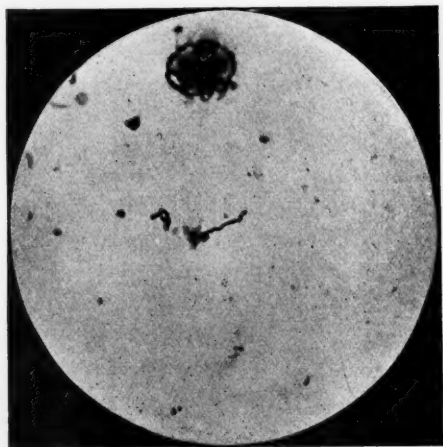


FIG. 7. Film from liver showing spirochaete-like structure.

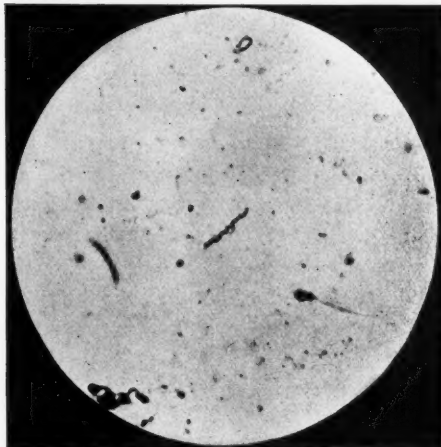


FIG. 8. Film from liver showing spirochaete-like structure.

DIASTASE DETERMINATIONS IN URINE AND BLOOD AS A METHOD FOR THE MEASUREMENT OF THE FUNCTIONAL CAPACITY OF THE KIDNEY

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Introduction.

THE activity of diastase varies with the pH of the medium in which it acts (1). In Wohlgemuth's method, in which untreated urine is mixed with unbuffered starch solution, the medium acquires the quite variable pH of the urine itself. Both Dodds (2) and Sladden (3) have shown that under these conditions the rate at which the starch is digested depends on the reaction of the urine as well as on the concentration of diastase in the urine. In view of the considerable increase in the accuracy of diastase determinations which has resulted from the recognition of this fact it seemed to us that diastase measurements in urine and blood plasma might be of some clinical value, particularly if the rate of excretion rather than the concentration of diastase were determined and if the effect on the rate of excretion of variations in the concentration of diastase in the plasma were known and eliminated. The conditions required for the quantitative measurement of diastase in urine were therefore studied in detail, and as a result we have developed a method which we think is somewhat more reliable than those described by Dodds or Sladden, but our principal object is to present data as to the value of the method as a means for estimating the functional capacity of the kidneys in patients with Bright's disease.

The Method.

The method is a modification of Wohlgemuth's technique. Varying amounts of urine are added to a starch solution, and the concentration of diastase is determined from the amount of urine required to digest the starch in a given time to such a degree that no blue colour is produced when iodine is added.

Michaelis and Pechstein (1) found that the pH at which diastase was most active varied with the salt content of the medium. In the presence of phosphates alone the optimum pH is 6.1, while when only chlorides are present the optimum is 6.7. Dodds accordingly brings the pH in his method to 6.1 because he adds phosphate, and Sladden titrates the urine to a pH of 6.7 because he adds chloride. But no account is taken of the phosphate and chloride in the urine itself, although the concentrations may be sufficient to convert their

pure phosphate or chloride systems into mixed phosphate-chloride systems. Under these circumstances the optimal pH would be somewhere between 6.1 and 6.7, though the chloride would have more effect than the phosphate. The actual concentrations are a matter of indifference so long as they exceed a certain minimum. But in the system used by Dodds there seems to be a danger of a disturbing variation in chloride concentration. Thus with a urine containing 1 per cent. of sodium chloride the first tube in his series would contain 0.12 per cent. chloride, which would be more than enough, but in his twelfth tube there would be only 0.003 per cent., which would probably be an ineffective concentration, and the optimal pH for this tube would be different from that required for the first tube. In Sladden's method there is always enough chloride, but in some of his tubes the phosphate concentration will be at a very low level. It seemed to us that it would be safer to make sure of a sufficient amount of both chloride and phosphate. This may be accomplished by using a starch-chloride-phosphate mixture which is prepared in the following way. An emulsion is made by stirring 4 gm. of soluble starch with a little cold water, adding 400 c.c. of hot water and boiling for ten minutes. After the addition of 6 gm. of sodium chloride the volume is made up to 1,000 c.c. with water. This starch-chloride solution is mixed with an equal volume of a phosphate solution prepared by dissolving 6.81 gm. of KH_2PO_4 with 86 c.c. of $\frac{N}{10}$ NaOH in water to a volume of 1,000 c.c. The phosphate solution can be made in bulk, but the starch-chloride solution must be freshly prepared each day.

This starch solution has a pH of 6.2. The buffer value of the phosphate it contains is amply sufficient to convert the reaction of any urine which is mixed with it to a pH of 6.2. In view of the fact that it contains 0.3 per cent. sodium chloride we expected that the optimal pH for the action of diastase would be about 6.5, but the optimum we actually found was between 6.1 and 6.5. Under the conditions we used, no differences in the rate of starch digestion could be detected with 6.2, 6.3, or 6.4. In all the determinations given in this paper a pH of 6.2 has been maintained.

Evans (4) has pointed out that the Wohlgemuth method often gives quite inaccurate results because there are such wide and relatively variable differences in the quantities of urine added to the starch. If a system of only twelve tubes is used to measure the diastase concentration of all urine samples, no matter how dilute or how concentrated they may be, no more than a rough approximation to the actual amount of diastase can well be expected. But we early found that the rate of diastase excretion was not influenced by variation in the rate of urine output. Therefore when the volume of an hour's urine was small we could be sure that the diastase concentration would be high, or if a large volume were obtained, that the concentration would be low. We therefore adopted the plan of eliminating all the large variation in diastase concentration which results from variation in the rate of water excretion by diluting our timed urine collections in such a way that the final volume for

each hour's collection of urine was 500 c.c. Another advantage which arises from working with such dilute urines is that the errors inherent in the pipetting of very small volumes of urine are avoided. We found that when amounts of urine so diluted of 1.5, 1.4, 1.3, 1.2, 1.1, 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, and 0.4 c.c. were used the diastase concentration of practically all urines, normal or pathological, could be determined.

The above amounts of urine were pipetted into twelve test-tubes. Water was added to bring the volume in each tube to 3 c.c. They were then immersed in a water-bath provided with a stirrer, which was regulated to a temperature of 37° C. A flask containing the starch-chloride-phosphate mixture was also put into the bath. When both the tubes and the starch solution had reached a temperature of 37° C., 1 c.c. of starch solution was added to each tube and the urine and starch mixed by inverting the tubes. The time was noted. Thirty minutes after the addition of the starch the tubes were removed from the bath

and 0.2 c.c. of $\frac{N}{200}$ I_2 was added to each tube with as little delay as possible.

The first tube which showed no blue colour was taken as the end-point.

The amount and the concentration of the iodine indicator is a matter of considerable importance. With stronger solutions or with larger amounts of

the $\frac{N}{200}$ solution the sharp transition from blue to an almost complete decolorization was not obtained. The indicator was prepared by dissolving 2.54 gm. of I_2 and 5 gm. of KI in 1,000 c.c. of water. This was made anew every week.

When diluted with three times its volume of water a $\frac{N}{200}$ solution is obtained.

This cannot be used for more than one day.

For the sake of uniformity we have expressed our results in terms of 'Wohlgemuth units'. A Wohlgemuth unit is the amount of diastase which will digest 1 c.c. of 0.1 per cent. starch solution in thirty minutes at a temperature of 38° C. to such a degree that no blue colour is obtained when iodine is added. Suppose we had a one hour's urine whose volume was 100 c.c. This had been diluted with water to 500 c.c. We found that 1 c.c. of the diluted urine digested 1 c.c. of 0.2 per cent. starch, and therefore this 1 c.c. of urine would have digested 2 c.c. of 0.1 per cent. starch and had a concentration of two Wohlgemuth units per 1 c.c. But the urine had been diluted five times with water, so the concentration of diastase in the original urine was 10 units per 1 c.c. Since the volume of one hour's urine was 100 c.c. the rate of diastase excretion was 1,000 units per hour.

The method used for the determination of the diastase concentration of blood plasma was almost identical with the urine method. The blood was drawn from an arm vein into a vaselined syringe containing a little powdered potassium oxalate. The cells were centrifugalized off and the plasma diluted to ten times its volume with water. The same system of pipetting was used as with the urine and the same starch-chloride-phosphate solution, but the time

of digestion was increased to one hour. On this account, if 1 c.c. of plasma diluted 1 in 10 digested 1 c.c. of 0.2 per cent. starch in one hour, it would have a diastase concentration of 10 units per c.c., since it would digest 10 c.c. of 0.1 per cent. starch in half an hour.

The accuracy of the method was tested by determining the time required for the digestion of starch by known dilutions of fluids containing diastase. It was found that the rate of starch digestion varied in direct proportion to the known diastase concentration. The method may therefore be regarded as quantitative. Reliable results may also be obtained with various modifications involving changes in the concentration of starch or in the time of digestion. Those we have given were chosen because they were convenient.

Diastase in the Urine and Blood of Patients with Bright's Disease.

It is a rather remarkable fact that almost all the published measurements of diastase in urine are given as concentrations of diastase and not as rates of diastase excretion. As a general rule the concentration of any substance in the urine is devoid of any physiological or pathological significance unless particular pains have been taken to observe conditions under which the concentration may be expected to approach the maximum. Since there is no evidence that any such precautions have been taken in the work which has been done with diastase it would seem likely that the diastase concentrations given in the literature are the resultant of two independent variable factors, the rate of diastase excretion and the rate of water excretion, and that the great variability in the rate of water excretion will deprive these diastase concentration values of any special significance. There are, however, certain substances, notably alcohol and oxybutyric acid, which the kidney is able to concentrate to only a small degree. On this account their rate of excretion usually runs fairly parallel to the rate of urine volume output. If diastase happened to be one of these substances the usual procedure of determining only the concentration in the urine might be justified in clinical work. This question is readily settled by varying the rate of water excretion and noting whether these variations are so paralleled by corresponding changes in the rate of diastase excretion that the concentration of diastase remains constant. An example of such an experiment is given in Table I.

TABLE I.

The Relation between the Volume of Urine and the Diastase Concentration of the Urine.

Time.	Volume of Urine. c.c. per hour.	Diastase Concentration. Units per c.c. of urine.	Rate of Diastase Excretion. Units per hour.
8.46-10.18 a.m.	255	4.0	1018
-10.50	844	1.5	1235
-11.34	614	1.3	767
-1.04 p.m.	220	5.0	1100
-3.58	143	6.7	952

In this and in other similar experiments the rate of diastase excretion remained at about the same level in spite of pronounced changes in the rate of volume of urine output, so that the diastase concentration was determined mainly by the rate of water excretion and varied approximately in inverse proportion to the volume of urine. It seems improbable, therefore, that the diastase concentrations found in samples of urine collected under uncontrolled conditions can be used as a reliable basis for deductions in regard to renal function. In this respect they would have much the same value as observations of the rate of urine output. We believe that the frequently observed association between low diastase concentrations and failure of renal function is largely due to the increase in the urine volume output which is common in terminal cases of renal sclerosis. But a low diastase concentration cannot in itself be taken as an indication of renal incapacity, for in any normal individual very low concentrations can be obtained whenever the volume of urine is increased by the administration of water.

Under certain special conditions, however, it is possible that the concentration of diastase in the urine might be taken as an index to the functional capacity of the kidney. It is known that the capacity of the kidney to produce high urinary concentrations of certain substances is impaired when a considerable part of the renal tissue has been destroyed by disease, and some relation might be found between the extent of the renal lesion and the highest diastase concentration which could be produced by the kidney. In order to force the kidney to concentrate the diastase the volume of urine must be reduced to a minimum. The plan we have followed is to keep all fluids from the patient from breakfast until the following morning. A twelve hours' collection of urine is made during the night, and the diastase concentration is determined in this specimen. It is improbable that we succeeded in attaining the maximum concentration in this manner, but there are difficulties in the way of requiring any more prolonged abstention from fluids in the case of certain patients, and under these conditions at least the gross fluctuations in diastase concentration which arise from variations in fluid intake are avoided.

On general grounds it might be anticipated that the rate of diastase excretion might be a better index of the functional activity of the kidney than the concentration of diastase in the urine. But its employment for this purpose would presuppose a knowledge of the factors which influence the rate. The few rates we have given in Table I show that in the same normal individual during a short interval of time the rate of diastase excretion may vary from 767 to 1,235 units per hour. These variations might be due to differences in the amount of diastase brought to the kidney for excretion or to many other causes than changes in renal activity. Therefore before the rate of diastase excretion can be used as an index of renal function, either the causes of these variations must be measured and their effects eliminated, or, if that is not possible, a sufficient number of rates on normal individuals must be determined to allow us to estimate the probable range of variation, so that we may not

TABLE II.

Variations in the Rate of Diastase Excretion in the same Normal Individual.

Date.	Time.	Rate of Diastase Excretion. Units per hour.	Diastase Con- centration. Units per c.c. of Urine.	Volume of Urine. c.c. per hour.	Notes.
Sept. 25	8.58 a.m.-10.19 a.m.	1340	5.7	235	9.0 a.m. Drank 1,500 c.c. of water 1.30 p.m. Diastase con- centration in plasma —7.14 units per c.c. 9.0 a.m. Drank 1,500 c.c. of water
	-11.00	1070	2.0	535	
	-12.20 p.m.	890	2.9	312	
	-2.45	1102	5.8	194	
Sept. 26	8.50 a.m.-11.16 a.m.	1248	6.7	187	9.0 a.m. Drank 1,500 c.c. of water 1.30 p.m. Diastase con- centration in plasma —7.14 units per c.c. 9.0 a.m. Drank 1,500 c.c. of water
	-11.59	1055	1.8	580	
	-12.49 p.m.	1002	2.5	401	
	-1.37	1102	3.3	331	
	-4.48	1290	15.0	86	
	-8.55	1082	13.4	81	
Sept. 27	-5.22 a.m.	732	13.3	55	
	-9.00	800	11.1	72	
	-1.25 p.m.	850	26.5	34	
	-8.02	932	18.3	51	
Sept. 28	-8.55 a.m.	826	16.5	50	
	-5.02 p.m.	1004	24.5	41	
Sept. 29	-12.16 a.m.	921	24.9	37	
	-8.04	1240	15.1	82	
	-12.17 p.m.	1140	18.1	63	
	-5.47	1116	28.6	39	
Sept. 30	-8.27	1168	11.1	105	
	-12.40 a.m.	1185	10.0	119	
	-6.54	1094	19.9	55	
	-12.12 p.m.	1070	33.5	32	
Oct. 2	6.10 a.m.-8.50 a.m.	889	22.2	40	9.0 a.m. Drank 1,500 c.c. of water
Oct. 3	-10.24	1426	6.7	214	9.0 a.m. Drank 1,500 c.c. of water 11.3 a.m. Took 10 gm. of a diastase prepara- tion which had a dia- stase value of 40,000 units in 500 c.c. of water
	10.32 a.m.-11.00 a.m.	2940	2.5	559	
	-11.32	1940	5.0	589	
	-12.07 p.m.	1410	3.3	581	
	-12.40	1290	2.5	566	
	-1.22	1500	2.8	454	
	-2.01	1460	2.5	600	
	-2.33	2620	2.9	512	
Oct. 4	-3.45	1530	3.3	787	8.19 a.m. Took 1,500 c.c. of water
	-5.17	1750	6.7	229	
	6.30 a.m.-8.19 a.m.	3020	8.4	209	
	-9.58	1925	25.0	121	
	-10.44	2170	16.7	115	
	-11.45	1660	2.8	756	
	-1.06 p.m.	1725	2.9	580	
	-1.55	2230	8.3	208	
Oct. 5	-4.12	1640	7.2	312	9.0 a.m. Took 1,500 c.c. of water 11.30 a.m. Diastase con- centration in plasma —12.5 units per c.c.
	7.00 a.m.-9.00 a.m.	2650	24.9	66	
	-10.25	1640	19.9	133	
	-11.09	1635	5.0	328	
	-1.44 p.m.	1390	2.9	572	
	-5.46	1580	11.1	125	
Oct. 6	-10.13	2110	24.3	65	
	6.3 a.m.-6.30 a.m.	1390	25.1	84	
	-8.21	1430	13.9	63	
	-2.44 p.m.	1440	14.3	100	
	-5.27 p.m.	1770	22.2	65	
			10.0	177	

interpret changes in the rate as due to pathological processes in the kidney when they may have arisen from causes which lie outside the kidney altogether. A series of diastase rates were therefore measured in a normal subject, and an attempt was made to correlate the observed fluctuations in the rate with various possible natural and experimental factors. These results are given in Table II.

It is apparent from the figures given in Table II that there is a considerable degree of variation in the hourly rate of diastase excretion, more than is found under appropriate dietary conditions for creatinine, but less than is usual for hourly rates of water, or chloride excretion. The measurements cover an almost consecutive period of time, and it will be noted that from October 3 onwards there is a general tendency towards an increase in the rate. It is probably only a coincidence that on that day the subject was given by mouth a diastase preparation which contained 40,000 units of diastase, for one of the highest rates was obtained just before it was taken. It is possible that these higher rates may have been due to an increase in the concentration of diastase in the blood. On September 25 the plasma contained 7.1 units per c.c., while on October 5, when the diastase rates were generally greater, a concentration of 12.5 units per c.c. was found, but this is little more than speculation. In general the results are only of negative value. Thus it is shown that there is no diurnal variation in the rate of excretion of diastase and there is no apparent relation to the periods of special activity in the pancreas. The independence in the rate of excretion of water and of diastase is repeatedly shown. But the physiological factors which influence the rate remain unknown, and in these circumstances all that can be done is to note that even rates as low as 732 units per hour are not necessarily due to any disturbance of renal function.

We were content with these fragmentary and inconclusive observations on diastase excretion under physiological conditions because in the meantime we had made some observations on the diastase excretion of patients with Bright's disease which gave an adequate answer to the question in which we were primarily interested—the possible value of the method as an index of the functional capacity of the kidney. These results are recorded in Table III.

In themselves the figures given above merely show that in patients with Bright's disease the concentration of diastase in the blood plasma varied from 10 to 20 units per c.c., that the rate of diastase excretion varied within the limits found in a normal individual, and that in these patients, as in our normal subject, the concentration of diastase in the urine was low when much water was taken and was considerably higher when fluids were restricted. But to determine whether or not these measurements have any clinical value they must be compared with some objective and if possible non-functional criterion.

It is necessary, however, to define clearly the meaning of the term 'clinical value' as applied to tests of renal function. For in many quarters there seems to be an impression that measurements of renal function have a value in and by themselves. Thus, for instance, when it is found that a patient can eliminate the usual amount of nitrogen and inorganic matter, or especially when it is

TABLE III.

Diastase Estimations in the Urine and Blood of Patients with Bright's Disease.

Name.	The Nature of the Renal Lesion.	The Extent of the Renal Lesion. Urea in one hour's Urine. Ratio: Urea in 100 c.c. of Blood. Percentage of Normal Renal Tissue.	Plasma Diastase Concentration. Units per c.c.	Rate of Diastase Excretion. Ingestion of Water. Units per hour.	Rate of Diastase Excretion. Abstinence from Fluids. Units per hour.	Urine Diastase Concentration. Ingestion of Water. Units per c.c.	Urine Diastase Concentration. Abstinence from Fluids. Units per c.c.
P.	Renal sclerosis	6	16.7	864	—	9.8	—
T.	Renal sclerosis	8	14.3	786	—	8.7	—
S.	Glomerular nephritis— diffuse	21	11.1	563	1092	12.5	36.4
B.	Glomerular nephritis— diffuse	28	16.0	1400	—	4.0	—
C.	Renal sclerosis	31	16.0	1400	—	12.1	—
G.	Nephrosis—cryptic	35	8.3	1000	—	4.7	—
Be.	Nephrosis—cryptic	45	10.0	1765	—	7.4	—
M.	Renal arterio-sclerosis	50	10.0	856	—	2.8	50.0
Gu.	Renal arterio-sclerosis	59	14.2	1406	1342	23.4	57.1
To.	Glomerular nephritis— diffuse	60	10.0	974	1252	2.6	26.6
Mo.	Nephrosis—pregnancy	60	11.4	1180	1514	5.5	66.6
R.	Renal arterio-sclerosis	63	16.0	2590	840	5.0	33.3
A.	Glomerular nephritis— focal	65	12.5	1290	—	3.3	—
Ca.	Albuminuria—cause ?	69	10.8	1168	794	23.3	44.4
L.	Glomerular nephritis— focal	71	11.1	1380	1095	2.8	57.2
M.	Albuminuria—cause ?	74	11.4	1330	—	6.3	—
A.	Glomerular nephritis— focal	76	16.0	2030	—	6.6	—
W.	Nephrosis—cryptic	83	11.1	1080	1110	2.7	22.4
Pi.	Albuminuria—cause ?	86	11.1	1440	1675	8.2	44.2
Br.	Nephrosis—cryptic	93	10.5	1084	—	3.2	—
Car.	Glomerular nephritis— focal	96	13.3	2110	—	3.6	—
An.	Nephrosis—pyogenic	102	20.0	2830	—	6.7	—
Le.	Glomerular nephritis— focal	107	11.1	1460	—	2.2	—
Tor.	Nephrosis—pregnancy	111	16.6	2310	—	4.8	—
W.	Albuminuria—cause ?	114	12.5	1785	—	3.9	—

found that the addition of nitrogen or salt to the diet is followed by a substantial increase in the rate of excretion, these facts are apt to be regarded as of clinical value in themselves, and even deductions in regard to dietetic treatment are based on findings of this nature. Yet it is a matter of everyday observation that patients whose kidneys are seriously disorganized by disease may excrete as much or even larger amounts of nitrogen and of salt than are commonly found in the urine of normal individuals, and further that any increase in the nitrogen or salt in the diet is followed by an increase in the rate of excretion of these substances. But there is practically no limit to the absolute amount of work the kidney is capable of doing. Under suitable conditions rates of water and of urea excretion which are considerably greater than the rates ordinarily observed in man can be attained by the small kidneys of the rabbit (5), and so patients whose kidneys have been almost entirely destroyed by disease may continue to excrete the usual amounts of nitrogen and are able to eliminate any additional nitrogen which may be added to their food. It can nevertheless be shown that their kidneys are functionally as well as anatomically defective, but the defect is relative, not absolute, for the significance of any measurement of function is to be found, not in itself, but always in its quantitative relation to something else. This 'something else' will vary with the objective of the observer. The physiologist, for instance, is interested in the relation between the kidney and its environment. He studies the manner in which the function of the kidney alters in response to the changes he experimentally produces within the body. These investigations are important to the clinician because they may help to explain the reaction of the kidney to pathological processes, but the centre of interest for him must lie in something more lasting than the everchanging adaptation of the work of the kidney to the shifting needs of the body. He must look for the permanent and irrevocable element in functional manifestations. This is to be found in the relation between the work of the kidney and its physical structure. And this relation must be quantitative, not qualitative, for the efforts to find any special mode of function which can be taken as indicative of a predominantly glomerular or tubular lesion have failed. What the clinician needs is a test of function which will enable him to determine the amount of secreting tissue in the kidney. This is a matter of primary importance for prognosis and treatment, and only tests which give this information can be regarded as having an immediate clinical value.

We have therefore compared the diastase values in patients with the results of a test which furnishes an approximate measure of the amount of secreting tissue in the kidney. Under certain special conditions the magnitude of the ratio between the rate of urea excretion and concentration of urea in the blood varies in direct proportion to the size of the kidney (6). The average ratio found in normal individuals is expressed as 100 per cent., and the degree of depression below this value in the ratios obtained from patients indicates the extent to which their kidneys have been rendered functionless by disease.

In Table III the results have been arranged in order in accordance with

this estimate of the amount of renal tissue still functioning. It will be noted that there is no parallelism with the diastase results. In the first two patients there was a marked retention of non-protein nitrogen in the blood (the concentration of urea in the blood was 229 mg. per 100 c.c. in P. and 184 mg. in T.), and yet the diastase concentration in the plasma was no higher than in other cases in which there was no nitrogen retention. In these cases also the rate of diastase excretion, though low, was still within the range of normal variation. In none of the other cases is there any indication of increase of diastase in the plasma, of decrease in rate of excretion, or of reduction in the diastase concentration of the urine at all parallel to the extent of the renal lesion. We therefore conclude that determinations of diastase either in the blood or in the urine of patients with Bright's disease have no clinical value.

TABLE IV.

The Relation between the Extent of the Renal Lesion and the Ratio:

Diastase in one hour's Urine.

Diastase in 100 c.c. of Blood.

Name.	The Nature of the Renal Lesion.	The Extent of the Renal Lesion.		The Diastase Ratio.	
		Ratio: Urea in one hour's Urine.	Percentage of Normal Renal Tissue.	Ratio: Diastase in one hour's Urine.	Percentage of Average Normal Ratio.
P.	Renal sclerosis	6	%	39	%
T.	Renal sclerosis	8		41	
S.	Glomerular nephritis—diffuse	21		38	
B.	Glomerular nephritis—diffuse	28		66	
C.	Renal sclerosis	31		66	
G.	Nephrosis—cryptic	35		94	
Be.	Nephrosis—cryptic	45		132	
M.	Renal arterio-sclerosis	50		64	
Gu.	Renal arterio-sclerosis	59		74	
To.	Glomerular nephritis—diffuse	60		73	
Mo.	Nephrosis—pregnancy	60		78	
R.	Renal arterio-sclerosis	63		122	
A.	Glomerular nephritis—focal	65		95	
Ca.	Albuminuria—cause ?	69		81	
L.	Glomerular nephritis—focal	71		93	
M.	Albuminuria—cause ?	74		87	
A.	Glomerular nephritis—focal	76		95	
W.	Nephrosis—cryptic	83		73	
Pi.	Albuminuria—cause ?	86		97	
Br.	Nephrosis—cryptic	93		87	
Car.	Glomerular nephritis—focal	96		119	
An.	Nephrosis—pyogenic	102		106	
Le.	Glomerular nephritis—focal	107		99	
Tor.	Nephrosis—pregnancy	111		104	
W.	Albuminuria—cause ?	114		106	

If the concentrations of diastase in the plasma and the corresponding rates of diastase excretion are compared, it will be noted that high rates are not infrequently associated with high plasma values and vice versa. The concentration of diastase in the plasma may very well be one of the factors which determine the rate, and if that is so rates of diastase excretion might be found to be related to the extent of the renal lesion when the effect of the variations in plasma diastase had been eliminated. This possibility had been foreseen, and the blood samples had accordingly been taken in the middle of the periods over which the rates were measured, so that each rate can be divided by the corresponding plasma concentration and the resulting diastase ratios compared with the urea ratios. These figures are given in Table IV.

There are indications here of some relation to the extent of the renal lesion, for the five patients with the lowest urea ratios have also low diastase ratios. But it would seem that the factor of kidney size has an effect on the diastase ratio only when there has been a very marked reduction in the amount of renal tissue, for in the remaining cases there is no semblance of any correspondence with the results of the urea ratio test. There are probably a number of other factors, besides the concentration of diastase in the plasma and the size of the kidney, which influence the rate of diastase excretion, and until these factors are known and their influence eliminated, diastase determinations cannot have any value as a method for determining the extent of the renal lesion in patients with Bright's disease.

Conclusions.

1. No relationship was found between the extent of the renal lesion in patients with Bright's disease and the concentration of diastase in the plasma and urine or the rate of diastase excretion.
2. When a large proportion of the kidney had been rendered functionless by disease there was a decrease in the ratio:

$$\frac{\text{rate of diastase excretion}}{\text{concentration of diastase in the plasma.}}$$

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THE ADENOID CHILD

A HISTOLOGICAL AND CLINICAL STUDY

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With Plates 14-16

THIS investigation of the adenoid child was undertaken at the suggestion of Dr. Scott Williamson, and we are indebted to Mr. Gay French for permission to investigate the cases in his department, and for the special clinical examination of many of them. The object of the research was to correlate the histological findings in the adenoids removed at operation with the varying deformities occurring in such cases, and possibly with metabolic abnormalities. The respiratory and chemical work has so far yielded negative or contradictory results, partly, we believe, owing to the difficulty of working with small children, and partly because, as we hope to show, at the time the work was begun, two distinct clinical entities were confused and considered as one. In view of the failure to obtain positive results, and as two distinct postural types were recognized in the children examined, the work resolved itself into a comparison of these types with the histological findings, and an attempt to correlate the clinical conditions and the histories therewith.

The children studied were all between the ages of 2 and 13 years. All were examined in the Ear, Nose, and Throat Department, diagnosed as suffering from enlarged adenoids, and entered for operation. In each case a detailed history was taken, and a special examination made by us, along lines which will afterwards be described, to supplement the full clinical notes taken in the department. In the later cases the relative size of the adenoid and nasopharynx was estimated at operation by a digital examination under anaesthesia. The material from about 200 cases was examined histologically, but as only 100 of these cases were studied in detail, these alone are included in this report.

The literature of the subject is so enormous that no *résumé* of it is attempted.

General Statement.

As a result of our investigations we find that children diagnosed as suffering from enlarged adenoids can be divided into two clinical groups associated with

(Q. J. M., Jan., 1924.)

distinct pathological changes in the adenoid tissue removed, viz.: I. A normal postural group. II. A hypotonic group.

Children in Group I have normal body curves, i. e. no postural abnormality. The adenoids removed show typical inflammatory changes, either acute or chronic, or, more frequently, both (Plate 14, Figs. 1 and 2).

In Group II the body curves are not normal, and the figures of the children are characterized by an exaggerated lumbar lordosis, associated with a pendulous belly and a general lack of tone (Figs. 3 and 4). The adenoids are hypertrophied as a result of an increase in the number and size of the follicles, and, though very frequently associated with a superadded inflammation, the hypertrophy remains a distinct histological picture.

The following is a brief description of the morbid anatomy of the two types; a more detailed account will appear in another paper.

Morbid Anatomy.

The amount of tissue removed at operation varies, and the size of the 'adenoid' has no direct relationship to the group mentioned. A large, definitely formed Luschka's tonsil is more likely to show true hypertrophy of the lymphoid tissue than inflammatory changes, but this is not always so, and the contrary does not hold. Fragmented material, on the other hand, tends to show inflammatory changes, but in many septic cases a large mass of inflamed tissue is removed.

In normal adenoid tissue the follicles are distinct, but not closely approximated, and there is a relatively large amount of interstitial tissue. There is a little fibrous tissue in the forms of strands supporting the vessels. The follicles are ringed with small lymphocytes; their germinal centres consist of palely staining cells, some showing mitotic figures, the lymphoblasts (Mallory (1)) or lymphoid haemoblasts (Latta (2)), others resembling and probably identical with the endothelial cells of the reticulum (1), called in future the endothelial cells. In addition, a few large endothelial phagocytes, staining still more faintly, normally occur in the follicles. The interstitial tissue is intersected by vessels, and consists of the same cell elements held together in the meshes of the reticulum, but the proportion of lymphocytes is increased and there are fewer endothelial cells. The large phagocytic cells found in the germinal centres are, however, never seen outside the follicles. A few plasma cells normally occur under the epithelium of the mucous membrane.

Acute inflammation (Plate 15, Figs. 5 and 6) is characterized by numerous haemorrhages and exudates. There is a great increase in the number of small lymphocytes, which are scattered throughout the tissue, but are accumulated in great numbers in the rings round the germinal centres—in some cases hardly any centre remains. The number of plasma cells, which are found not only under the mucous membrane, as in the normal, but also throughout the tissue, is also largely increased. Organisms are present both in the surface exudates and in the crypts, and also, in a few cases, in the follicles. The vessels may be engorged.

Polymorphonuclear leucocytes are only rarely seen, and then in the vessels or in the exudate.

Chronic inflammation (Figs. 7 and 8) shows a different picture. The changes found in acute sepsis are carried a degree farther. There is an even greater proliferation of the lymphocytic elements, and there may be difficulty in distinguishing the follicles. There is a marked increase in the fibrous tissue, especially round the vessels and under the mucous membrane. The follicles may be ringed with fibroblasts, or at least with cells showing similar staining properties. In extreme cases a large pad of tissue may consist almost entirely of thickened blood-vessels, with a little interstitial tissue packed with small lymphocytes and with practically all the follicles destroyed or replaced by small lymphocytes.

In the hypertrophied adenoid (Plate 16, Figs. 9 and 10) the histological findings are entirely different from both the above. The most striking feature is the enormous increase in the number and size of the follicles, and, relatively, of the germinal centres. The ring of lymphocytes is often hardly appreciable, whereas the endothelial cells of the germinal centres are enormously increased, especially the large phagocytic endothelial cells. Under the low power the germinal centres have a sieve-like appearance, owing to the number of these poorly staining macrophages. There is little interstitial tissue and no increase in fibrous tissue. No organisms are found.

Uncomplicated cases of hypertrophy are rare, a greater or lesser degree of inflammatory change being usually observed. We wish, however, to lay stress on the fact that, in spite of the superadded sepsis, the original hypertrophy remains as the essential histological feature, differentiating this group from the purely inflammatory type.

It is, perhaps, worth recording that tubercle was found in only one of the adenoids examined.

The tonsils removed from the same cases were not examined in such detail, but sections were made of nearly all, and these showed similar changes to the corresponding adenoids.

Postural Changes.

The children were examined completely undressed. A graphic method of recording and measuring was obtained by the use of the simple apparatus shown in the photographs. The lighting is from two Cooper Hewitt mercury vapour lamps hung on the side of the grid. The camera and apparatus are so arranged that there is no measurable distortion when grid and child are in focus, so that, as each square measures 2.5 cm. each way, direct measurements can be made. When possible, the children are so arranged that a perpendicular through the centre of the external malleolus passes just behind the ear. This cannot always be done, as some children, especially those belonging to Group II, are not in equilibrium in this position. Figs. 1 and 2, Plate 14, show typical members of the *inflammatory group*. The figure is normal and has the following characteristics: (1) The long axis of the trunk is approximately perpendicular. (2) The

anterior and posterior outlines of the trunk as seen in profile are flat curves. (3) A perpendicular through the middle of the external malleolus passes in front of the most anterior point on the dorsal curve. (4) The lordotic angle is wide (i. e. the angle made by lines joining the angle of the scapula to the point of maximum lordosis and the latter to the most posterior point on the buttock curve). 82 per cent. of the photographs of septic cases show an angle between 145° and 160° . (5) The maximum belly, i. e. the most protuberant point on the abdominal wall, is either on a level with, or above the level of, the point of maximum lordosis. In small children the maximum belly is generally the most anterior point, but in older children the chest should project farther forward. (6) This group, as a whole, has good muscle-tone.

Sixty-one out of 100 children had this type of figure—in 51 cases the material removed showed predominantly inflammatory changes; in 10 cases the histological picture was one of hypertrophy. Put in another way: 58 cases gave a histological diagnosis of inflammation; of these, 51 were correctly diagnosed, whereas 7 were placed on postural grounds in the hypotonic group and so were incorrectly diagnosed.

I. *Normal Postural Group.*

Normal Posture.

83 per cent. simple inflammation of adenoids.
17 per cent. hypertrophied adenoids.

Inflamed Adenoids.

88 per cent. correctly diagnosed on posture.
12 per cent. incorrectly diagnosed on posture.

Children of the *hypotonic type* (Figs. 3 and 4) have a very different figure. The characteristic features are: (1) The long axis of the trunk is tilted so that it is no longer perpendicular, but slopes from below backwards, i. e. the shoulders and upper part of the trunk are thrown backwards, while the lower part comes forward over the pubes. (2) The curves of the anterior and posterior outlines of the body are less flat than the normal. In certain cases the lordosis is very marked. (3) A perpendicular through the middle of the external malleolus passes behind the most anterior point on the dorsal curve. (4) The lordotic angle is less obtuse—in 74 per cent. of the cases belonging to this group between 132° and 144° . (5) The maximum belly is generally well below the level of the maximum lordosis; in fact, a pendulous belly is characteristic of this group. (6) The group, as a whole, appears to have a lack of muscle-tone; the child is hypotonic. The hypotonus would account for the posture, which is due, probably, to the pendulous belly of the flabby child producing a compensatory tilt of the trunk.

Forty cases had this type of figure—of these, 33 had essentially hypertrophied adenoids, and 7 had inflamed adenoids only. Or, on the histological diagnosis, 42 cases in the series showed hypertrophied adenoids; of these, 31 were correctly diagnosed, whereas 9 cases had a normal figure and so were incorrectly diagnosed.

*II. Hypotonic Group.**Abnormal Posture.*

82.5 per cent. hypertrophied adenoids.

17.5 per cent. inflamed adenoids.

Hypertrophied Adenoids.

79 per cent. correctly diagnosed on posture.

21 per cent. incorrectly diagnosed on posture.

The total diagnosis on posture, including both groups, gives 15 per cent. incorrect and 85 per cent. correct.

It does not seem out of place here to refer to the 'adenoid deformities of the chest' of the text-book. These deformities include Harrison's sulcus, pigeon chest, winged scapulae, &c., and are described as due to nasal obstruction. At one time we associated these more particularly with the 'inflammatory' group, but an analysis of our completed cases does not confirm this, as these deformities occur in both groups. We are still of the opinion, however, that with a larger series they would be found associated to a much greater extent with inflammatory conditions, as these are more likely to cause respiratory obstruction.

These chest deformities are almost invariably associated with the stigmata of rickets—knock-knees, bowed tibiae, bossed head, &c., the association of marked knock-knees with the chest deformities being very remarkable. These cases had nasal obstruction, but many others had nasal obstruction and no such deformities; in fact, it seems clear that nasal obstruction, or, for that matter, any obstruction to respiration, does not produce these deformities without an accompanying softening of the bones. The correlation of these deformities with adenoids is due, in our opinion, to the fact that an enormous proportion of adenoid subjects are rickety. One authority, for example (Biaggi (3)), states that 90 per cent. of the cases in an institute for rickety children had adenoids.

Histories and General Clinical Findings.

In spite of the general inaccuracy of the histories that can be obtained in an out-patients' department from the relations, a definite connexion can be shown between the septic group and a history of colds, nasal trouble, bronchitis, and the 'wet diathesis'. 87.5 per cent. of this group gave such a history. In comparison, the histories of some of the 'hypotonic' group are of interest. Naturally a large number of these came up because of a recent superadded acute sepsis (56 per cent.), and if the diagnosis were made only on the history and the throat condition, these cases would be incorrectly diagnosed. Others, however, were admitted to the department because, in the course of the routine examination, enlarged tonsils had been noticed. Some of these, and among them intelligent people, gave no history suggesting nasal or post-nasal trouble or any of the ordinary adenoid symptoms. We say 'ordinary' because, if it were possible to read the entire literature, it is doubtful whether any conceivable symptom would not be included in an exhaustive list of those occurring in adenoid children.

An inquiry into diet and home conditions was made, but the details were not sufficient to be of value.

Owing to the size of the department it was inevitable that the cases should be examined by different members of the staff, and it has therefore been impossible to correlate those clinical findings, as, for example, the size of the tonsil relative to the fauces, which have a personal factor. The following observations are, however, suggestive.

There is a definite sex incidence—59 per cent. of the cases are boys, 41 per cent. girls.

The so-called adenoid facies, i.e. open mouth, short upper lip, broad nose with poorly developed alae, &c., is, in our experience, definitely associated with nasal trouble, e.g. hypertrophied turbinates, chronic nasal catarrh, &c. It appears that intranasal obstruction *per se* has more to do with the production of this expression than the actual presence of enlarged adenoids. Indeed, a digital examination in many of these typical cases revealed the presence of only a small pad of adenoids. Sir St Clair Thomson (4) prefers to call this facies 'the facies of the mouth-breather', but our observations would seem definitely to relate it to intranasal obstruction.

Discussion.

We are of the opinion that the evidence set out in the preceding paragraphs justifies the statement that children diagnosed as cases of adenoids are suffering from one of two distinct pathological conditions: (1) Simple inflammation of the nasopharynx, and (2) true hypertrophy of the adenoid tissue, which can, in the majority of cases, even if complicated, be distinguished clinically. When the condition is an uncomplicated simple inflammation, the symptoms are local, apart from the immediate general reaction to an acute infection (temperature, &c.). The body type is normal, and the response in the adenoid tissue is an increase in the number of small lymphocytes and plasma cells, and later in the amount of fibrous tissue—the ordinary response of lymphoid tissue to local sepsis.

In the second condition the symptoms are vague, apart from those due to superadded sepsis, when present, but the abnormal posture previously described is typical of this condition. The fundamental tissue change is a hypertrophy of the endothelial elements of the lymphoid tissue of the nasopharynx, with no increase, and possibly a decrease, in the small lymphocytes in uncomplicated cases. The significance of this hypertrophy, apart from any added inflammatory change and its associated postural changes and hypotonus, remains to be determined.

Dan M'Kenzie (5) states that the cause of the hypertrophy is unknown, 'but modern opinion tends to the belief that the hypertrophy . . . is a reaction to septic infection of the nose and nasopharynx'. It would appear from the context that the reference is to uncomplicated hypertrophy. Barnes (6) also states that there is no definite knowledge as to the cause of hypertrophy, but adds that it is

probable that prolonged irritation may cause it, though often there is no assignable reason for it. Before accepting the dictum that it is a reaction to septic infection, due consideration must be given to the fact that the infection producing it is undoubtedly of a different order from that causing the histological picture of chronic sepsis seen in the purely inflammatory cases. Further, it is difficult to attribute the accompanying general hypotonus to a local sepsis, more especially when there is no evidence of nasopharyngeal trouble. The constant association of a hypotonic condition with hypertrophy of the lymphoid tissue of the throat suggests rather some underlying general metabolic or infective condition as the cause of both.

Mallory (7) states that an increase in the endothelial elements in the lymph nodules of lymph glands is frequently a result of a blood-borne toxin—that is, it is a result of a general condition. This theory would explain our findings in the second group more easily, though we are completely ignorant as to the nature of the stimulus that produces the change.

As the hypotonic cases suggested a general condition, and as no obvious defects could be found, we investigated the possibility of a dietetic or hygienic factor, but as yet we have not been able to establish one. Cramer's (8) work on the lymphocyte in nutrition is of interest in this connexion. He points out the atrophy of lymphoid tissue and the decrease in the number of small lymphocytes in conditions of failure in the supply of water-soluble B vitamin associated with a failure of nutrition. At other clinics a hypotonic child is recognized and associated with a faulty diet. We have not yet been able definitely to connect this child with the one described, but we hope that future work will throw light on this subject. For the present we cannot do more than indicate the nature of the pathological changes in the adenoids and correlate these with the postural deformities, leaving aetiology and treatment for the future to elucidate.

Summary.

1. Two distinct pathological conditions are found in the material removed, viz. an inflammatory condition characterized by an increase in the small lymphocytes and the fibrous tissue, and a condition of hypertrophy distinguished by an increase in the number and size of the follicles and a decrease in the number of small lymphocytes.

2. These two pathological conditions are related to two corresponding clinical types, since children with normal figures and marked nasopharyngeal sepsis have inflamed adenoids, while those with the hypotonic figure have hypertrophied adenoids, primarily without inflammatory changes.

3. The diagnosis is made on the type of child, but the septic type is frequently suggested by the history.

4. Deformities of the chest occur in both groups, but are definitely related to rickets, since other deformities are present, and the respiratory obstruction alone is not sufficient to produce them.

5. The adenoid facies is the facies of intranasal obstruction.
6. The aetiology of the hypertrophied adenoid is obscure—the associated clinical type suggests a general condition.

We have to thank Mr. Gay French for the whole-hearted support he has given to the work, without which it could not have been carried through, and the members of the Ear, Nose, and Throat Department for their help and interest. We are particularly indebted to Miss Stella Glascock for the care and skill with which she has prepared the material for this research, and for her help in many other ways.

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DESCRIPTION OF PLATES.

PLATE 14, FIG. 1. A boy, aged 8. Typical member of the inflammatory group. Normal figure.

FIG. 2. A girl, aged 8. Typical member of the inflammatory group. Normal figure.

FIG. 3. A boy, aged 8. Typical member of the hypertrophied group. Hypotonic figure.

FIG. 4. A girl, aged 8. Typical member of the hypertrophied group. Hypotonic figure.

PLATE 15, FIG. 5. Microphotograph of acutely inflamed adenoid showing:

1. Heavy ring of lymphocytes round germinal centres.
2. Exudate.
3. Increased number of plasma cells under mucous membrane.

Magnification $\times 50$.

FIG. 6. Microphotograph of a germinal centre from an acutely inflamed adenoid showing:

1. Heavy ring of lymphocytes.
2. Decrease in size of germinal centre.
3. Absence of large phagocytic endothelial cells.

Magnification \times approximately 400.

FIG. 7. Microphotograph of a chronically inflamed adenoid showing:

1. Lymphocytic proliferation and disappearance of follicles.
2. Increase in fibrous tissue.

Magnification $\times 50$.

FIG. 8. Microphotograph of vessels from a chronically inflamed adenoid showing:

1. Thickening of the vessels.
2. Tissue packed with lymphocytes.

Magnification \times approximately 250.

PLATE 16, FIG. 9. Microphotograph of an hypertrophied adenoid showing:

1. Increase in number of follicles.
2. Narrow rings of lymphocytes.
3. Large germinal centres.
4. Numerous large phagocytic endothelial cells in germinal centres.

Magnification \times approximately 150.

FIG. 10. Microphotograph of a germinal centre from an hypertrophied adenoid showing:

1. Large number of poorly staining large phagocytic endothelial cells.

Magnification \times approximately 400.

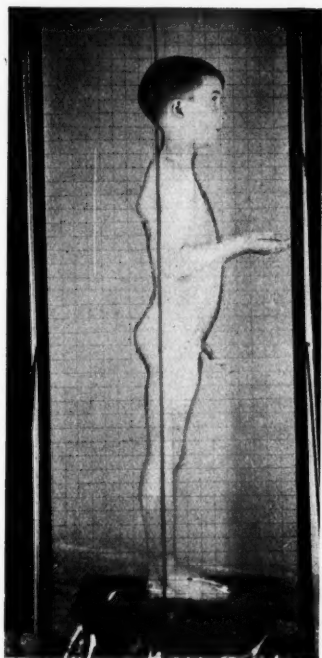


FIG. 1

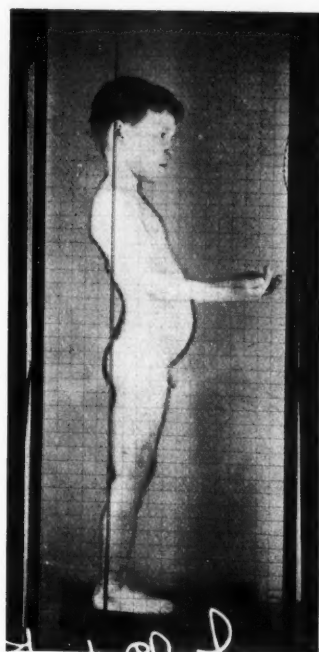


FIG. 3

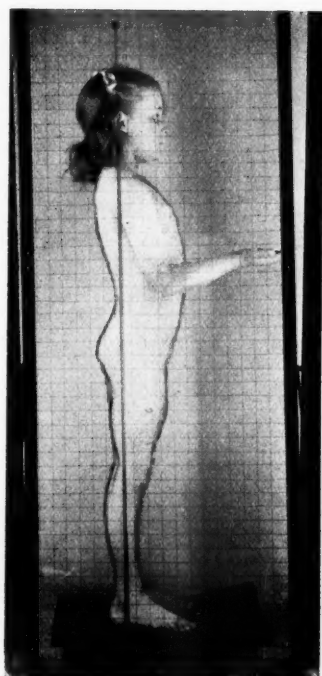


FIG. 2

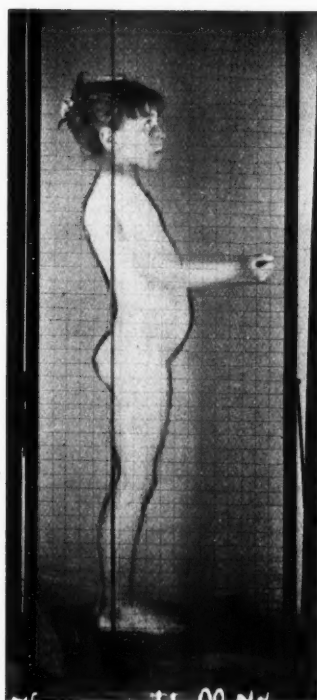


FIG. 4

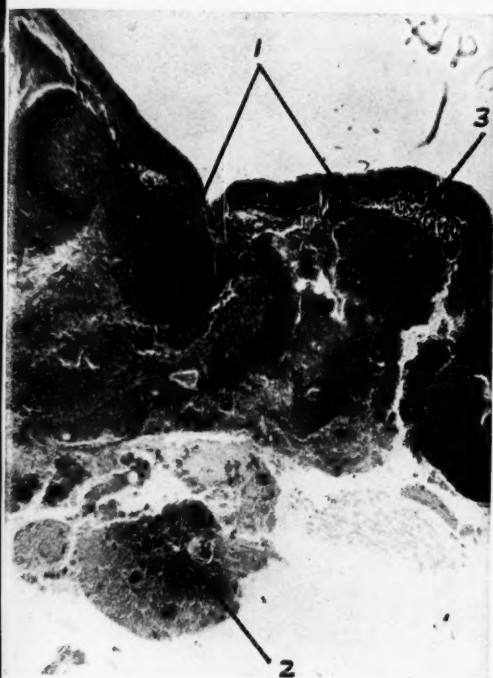


FIG. 5



FIG. 7

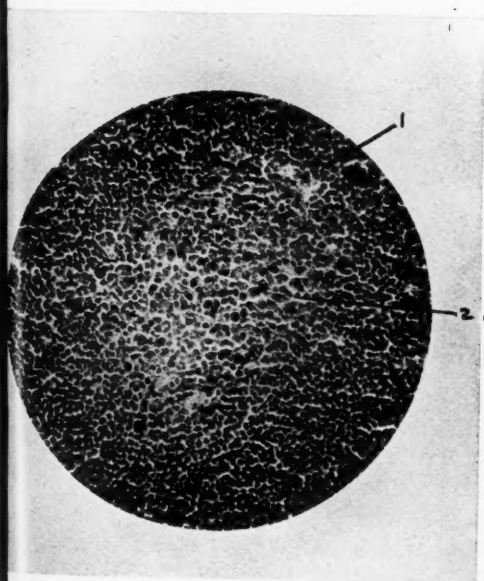


FIG. 6

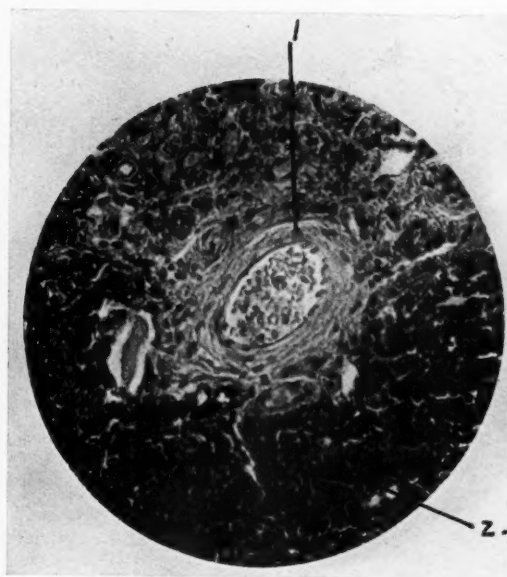
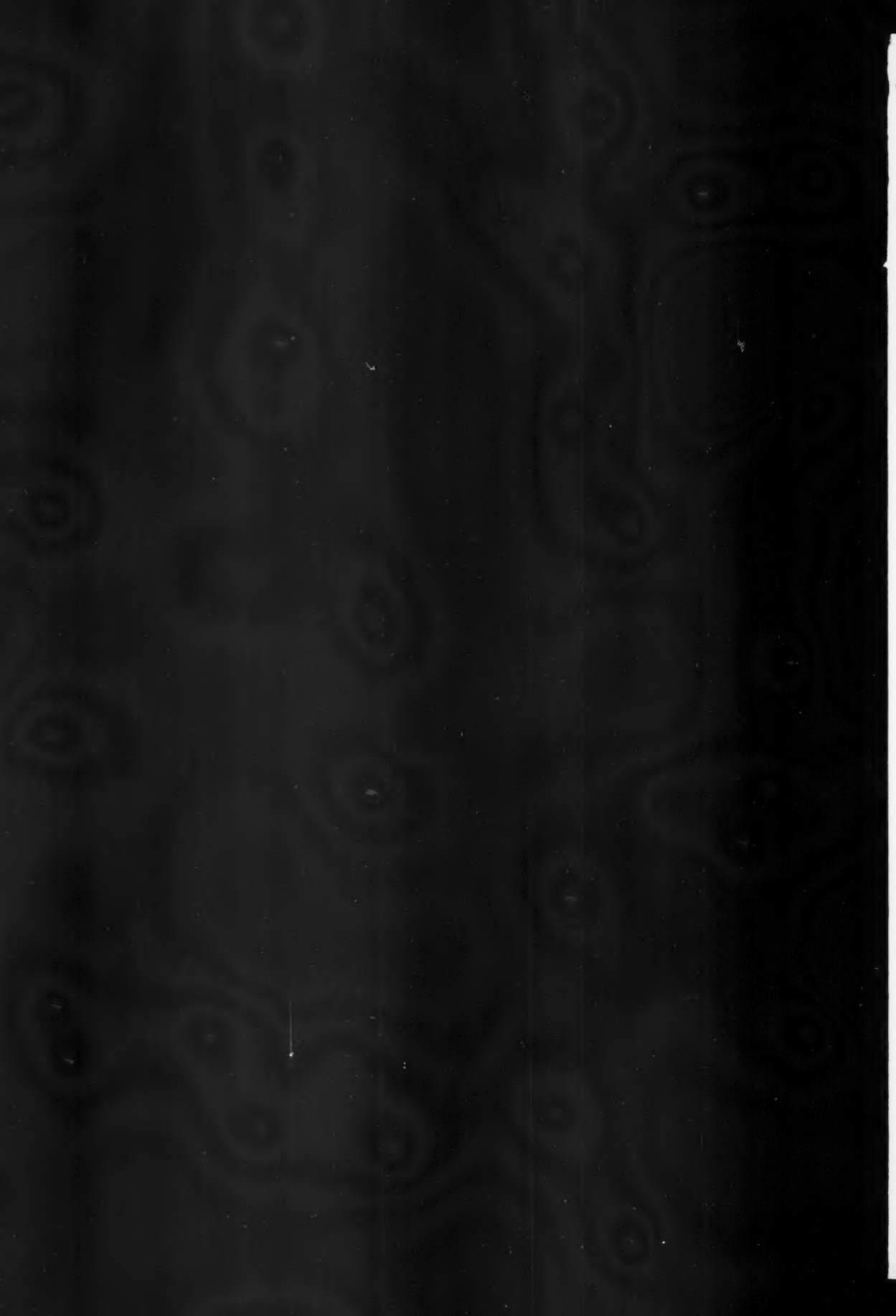


FIG. 8



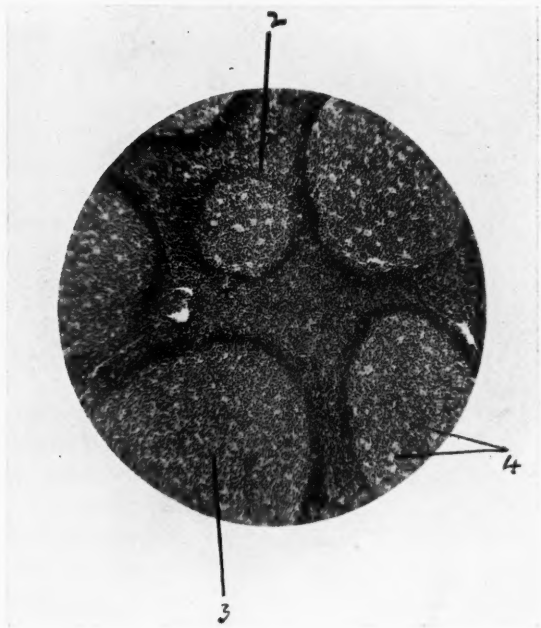


FIG. 9

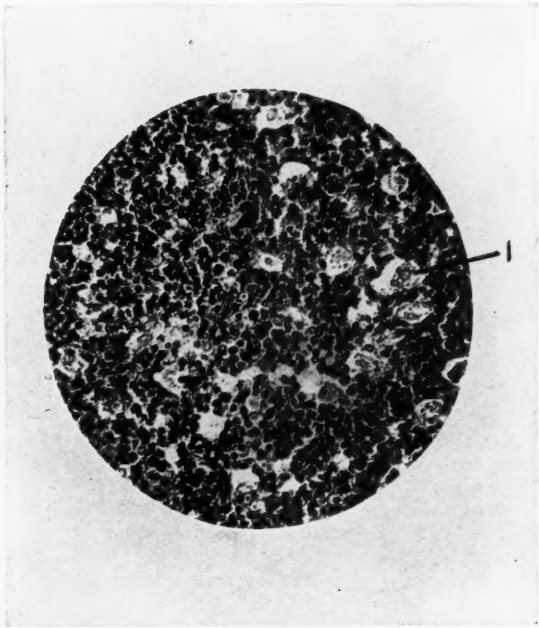


FIG. 10

ARTHROPATHIA PSORIATICA

BY ARCHIBALDE GARROD AND GEOFFREY EVANS

THE occurrence of joint lesions in a certain number of cases of psoriasis is well known and the subject has long been one of particular interest to the French School of Medicine. Alibert in 1822 (quoted by Menzen) seems to have been the first to recognize the occurrence of joint pains in psoriasis. Bazin (1) in 1860 made a distinction between cases of psoriasis with joint lesions, which he named psoriasis arthritica, and those without joint lesions, which he termed psoriasis herpetica. Many observers have established the psoriasis and arthritis syndrome since this date, and it has been discussed in some detail by Kutzmitsky (2), Waelsch (3), Brocq (4), Menzen (5) and Bourdillon (6). More recently Adrian (7) reported a case in detail and collected much of the literature on the subject; under the title of 'arthropathia psoriatica' this author demonstrated the syndrome as a clinical entity and showed that the concurrence of skin and joint lesions is not merely a coincidence as Pollitzer (8) suggested.

The following three cases are placed on record both because they are classical examples of the association of psoriasis and arthritis, and because they illustrate other interesting aspects of the disease; thus trauma was an exciting cause in one case, in two cases there was pronounced menstrual disturbance, and in two cases the clinical picture was complicated by intermittent hydrarthrosis.

Case Reports.

Case I. F. D., female, aged 31, music-hall artiste, single.

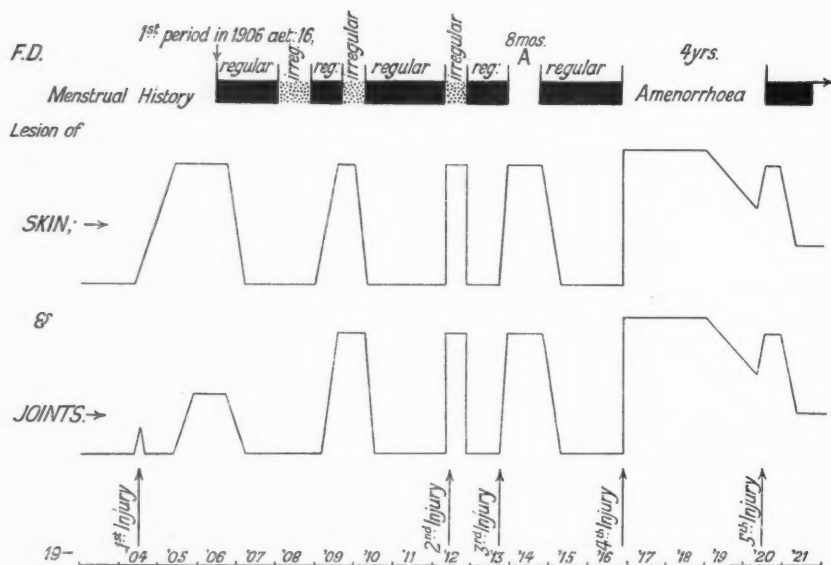
In 1904, at the age of 14, while training for some sports, the patient fell on her left knee. One or two weeks later she had to go to bed on account of swelling of the knee, and at the time of the first appearance of the swelling she became aware of a small red patch, moist and irritable, on the extensor aspect of the knee; her attention was called to this patch by the irritation. It was the first appearance of both the skin and joint affection. A diagnosis of traumatic synovitis was made. After two weeks in bed the swelling of the knee subsided and she made a good recovery, excepting that the knee was left a little stiff. The erythema, however, gradually spread, first to the other knee and then all over the body, involving the forehead and scalp, but not the face. A year later the skin condition was at its worst; the eruption was moist and wept, and appears to have assumed the character of an exfoliative dermatitis. The rash remained bad for about two years and then disappeared. Three years after its onset it was completely healed. A year after the accident, when the psoriasis was at its worst, a polyarthritis developed. Swelling of the left knee was

followed by swelling of the right ankle, then successively the right knee, left ankle, and both elbows became affected. The left knee and right ankle suffered most; they remained stiff and swollen for a year; they were subject to improvement and relapse, but they were never so severely affected as to necessitate rest in bed.

During 1907 and 1908 she was in good health and able to pursue her vocation of music-hall artiste, which involved dancing. There was no rash and no stiffness of the joints.

In 1909, gradually over a period of six months, swelling and stiffness of the left knee-joint recurred with increasing severity accompanied by reappearance of the rash, which first appeared on the left knee. In February 1909 she was admitted as an in-patient to the Middlesex Hospital under the care of Dr. W. E. Wynter, and on September 30, 1909, she was admitted to St. Bartholomew's Hospital under the care of one of us (A. E. G.). Since that date she has been under more or less continuous observation. On the occasion of her first admission she had the appearance of a patient suffering from the most severe form of

CASE I.



crippling arthritis, and the swelling of the knee-joints was observed to be an intermittent hydrarthrosis. The condition at this time was reported by Dr. Whitehead Reid (9). On her discharge from hospital in February 1910 recovery was almost complete; the psoriasis was completely healed, the joints were only a little stiff and they soon became free and supple. On September 10, 1910, she reported for examination; the knees showed no sign of disease, the fingers were a little swollen and stiff at the terminal interphalangeal joints, and there was no rash; she felt quite well and could walk 15 miles in the day. She resumed her work again as a music-hall artiste.

On April 14, 1912, she slipped while dancing and felt her ankle snap. The joint swelled immediately and swelling of the left knee soon followed. A week later the psoriasis reappeared. On admission to hospital, on April 24, there was widespread psoriasis and polyarthritis. On September 23, 1912, she was discharged cured and returned to her work on the stage.

She remained in good health until one Saturday evening in September 1913 when she sprained her ankle in jumping 10 feet from a window-sill to the ground. Two days later the right ankle was stiff and she felt cold and shivering though the weather was warm. A few days later, when sitting on the beach, she was suddenly overcome with helplessness and had to be carried to her lodging. Two days after the accident the psoriasis appeared as a spot on the right knee, and two days later she was unable to complete her performance on account of a feeling of malaise and of imminent 'unconsciousness'. The psoriasis spread rapidly over the limbs and trunk and a multiple arthritis developed, namely pain and swelling of the right ankle, left knee, right knee, left ankle, both elbows, and the interphalangeal joints of hands and feet, particularly the fingers. On admission to hospital, in November 1913, there was a widespread scaly eruption extending in large irregular areas over the upper and lower limbs, chiefly on the extensor aspects and involving the finger-nails; there was an effusion into both knee-joints and marked stiffness and pain on movement in many other joints. The intermittent character of the swelling in the knees was not evident, but over a period of several months the temperature chart showed a slight rise lasting two or three days and occurring every week; it was thus evident that the recurrent element was still present, though in only a slight degree. She was nearly well on her discharge in July 1914, and she gradually made a complete recovery.

Early in 1915 she returned to work and stated that she never felt so well as at that time. In September 1916 three medical officers passed her as fit for munition work.

A week later she was knocked down unconscious by a tramcar and sustained injuries to the head. She has been ill ever since and is now crippled with chronic arthritis. Following the accident there was loss of memory for recent events, and she did not recover her memory until February 1919. Almost immediately after the accident the joints became increasingly stiff and painful and the psoriasis recurred concurrently or soon after. She became increasingly ill and the rash spread until there was 'scarcely a whole patch of skin' left. She was reduced to so wretched a plight by pain and sleeplessness that she attempted to end her life by taking a bottleful of aspirin tablets. She was admitted to Camberwell Infirmary. The disease progressed; she became weak and emaciated and suffered greatly. In October 1918 she was admitted to St. Bartholomew's Hospital under the care of Dr. Langdon Brown. All joints were affected with the exception of the hips and shoulders, which have escaped throughout; elbows, wrists, knees, and ankles were severely affected and there was scarcely any movement in these joints; there was pain in the sterno-clavicular joints, pain and stiffness in the temporo-mandibular joints, and also in the cervical and upper dorsal regions of the vertebral column. The interphalangeal joints were severely affected, the distal joints being flexed and the proximal joints hyperextended. The affected joints showed periarticular thickening, redness, and, in the larger joints, effusion. Muscular wasting was marked and the patient lay on her back in bed unable to raise herself. Only the face remained clear of psoriasis. Improvement began to occur in January 1919, and she was discharged improved in February.

In June 1920 the knees were forcibly bent by accident, they were heard to 'snap', and from this date the joints and psoriasis began to get worse again. She was admitted to hospital in August 1920. She was pale and ill-nourished and covered with an extensive psoriasis which spread over the anterior abdominal wall and right breast, and covered both buttocks, the right loin, left leg and knee, both elbows, hands, and nails. The knee-joints were stiff and swollen, but could be fully extended; the ankle and tarsal joints were stiff and swollen, the elbows, wrists, and metacarpo-phalangeal joints were also affected. The carpo-metacarpal joints were normal; the proximal interphalangeal joints were hyper-

extended, the distal interphalangeal joints flexed. The movements of the neck were limited, especially those of rotation; the rest of the spine was normal, and the hip- and shoulder-joints were unaffected. By August 30 there was great improvement in all joints, and on September 14 a menstrual period lasting four days was completed, this being the first menstrual period for four years.

In the following week, on account of pain and other physical signs in the right iliac fossa, chronic appendicitis was diagnosed, and appendicectomy was performed on September 17. The appendix showed evidence of chronic inflammation. Improvement in the general condition was maintained and the patient was discharged on December 13, 1920. Since that date her general health has been good, there has been no relapse, and there has been a slow improvement in the mobility of the joints. She remains, however, crippled with arthritis, able to use her fingers and hands a little and to walk with difficulty.

The patient was seen on several occasions by Dr. H. G. Adamson, who confirmed the fact that the skin lesions were psoriasis. The joint lesions were of the type of chronic infective arthritis. The character and distribution of the joint lesions has been described in detail and certain facts bearing on the subject require further notice. There was nothing in the past history or family history of the patient to throw light on the complaint. In particular there was no past history of rheumatic fever, rheumatism, or chorea, nor was there a history of tonsillitis. At no time in the course of this long illness was there any sign of affection of the heart, lungs, or kidneys. The possibility of a focal infection was always under close consideration. There was no history or clinical evidence of gonococcal infection. Infected teeth were removed at an early period in the course of the illness. A fistula in ano was treated surgically by Major McAdam Eccles in 1917; previously there had been no sign of this complaint. So long as we have known the patient there was a slight dyspepsia, and this was finally attributed to a chronic appendix. This possible focus of infection was often in mind, but there were never in previous years definite clinical signs of its existence. At the time of its removal recovery from the last attack was well advanced, and the patient had started menstruating again—a sure sign of her improvement. In fact, though chronic appendicitis is known to be a cause of chronic arthritis in some cases, we hesitate to regard it as of importance as an aetiological factor in this case.

The general condition of the patient in the relapses of her complaint was that of one suffering from a severe toxæmia. There was no significant alteration in the blood count—blood counts were done in both active and quiescent periods—and, apart from a slight degree of secondary anaemia, the counts were normal both as regards total numbers and differential counts. In the acute stage of a relapse the patient was ill and wasted and the disease was accompanied by fever and increased pulse-rate.

This type of arthritis with profound constitutional disturbance, occurring as an acute affection without discoverable cause and in a young woman, closely approximates to the clinical picture of rheumatoid arthritis (10). The present case, however, belongs to a different category, and its close association with psoriasis in its onset, recovery, and relapses marks it a case of arthropathia psoriatica.

The case is of interest in several other respects. In the first place a condition of nervous instability is sufficiently often observed in psoriasis to have led to a neuropathic theory of the complaint. Our patient has a highly-strung and nervous temperament. She has not always been dependable upon in her speech and actions, and on one occasion she attempted to take her life; in addition there is one physical sign of nervous disturbance in the presence of a coarse lateral nystagmus, at first only present when under observation, but later evident at any time on conjugate deviation of the eyes to either side. In the second place it is a remarkable fact that the onset of the complaint and each relapse,

excepting the second, were immediately preceded by trauma. The relation of trauma to psoriasis is referred to by several observers (5.11.17), but we have not found any record of a case in which injury was closely associated with repeated attacks of arthropathia psoriatica as in the present case.

The nature of the injury, too, is significant; on three occasions it was a sprained joint, on the fourth occasion it was so severe an injury as to almost certainly have involved damage to a joint. Abdominal section and appendectomy in 1920 did not precipitate an attack, and we incline to the view that in the case of our patient injury to joints was the determining cause of the disease. In the third place there was disturbance of menstrual function in this patient. Menstruation commenced at the age of 16, and may have been delayed by the first attack of the disease, which lasted from 14 to 16 years of age. Menstruation was irregular in 1908 during a period of good health; it was regular during all succeeding periods of good health; it was irregular and scanty towards the end of the second relapse, it was irregular and scanty throughout the third relapse, there was amenorrhoea during the fourth and fifth relapses. The coincidence of menstrual irregularity with the joint and skin lesions is shown on a chart (p. 172). The association of psoriasis with menstrual function is well known. Thus Petrini (12) has recorded the case of a woman aged 28, who suffered from psoriasis for six years, in which interval of time the rash disappeared in every one of five pregnancies. In other cases it is not uncommon to see psoriasis develop at the time of the menses, pregnancy, or parturition (13). We have found no record of disturbed menstrual function in recurrent attacks of psoriasis such as occurred in this patient, with resumption of normal menstruation in the intervals of recovery from the skin and joint disease. Finally, there is the introduction into the clinical syndrome of intermittent hydrarthrosis (14), a complication seldom met with in such cases. It is possible that this curious complication may ultimately throw some light on the nature of the complaint. One of us (A. E. G.) has long been of the opinion that many of the phenomena of intermittent hydrarthrosis are capable of explanation in terms of a condition of body hypersensitiveness, and the intermittency of the joint-swellings in intermittent hydrarthrosis seems comparable to the intermittency observed in many cases of spasmodic asthma (15). In the same connexion it is of interest to refer to Whitfield's (16) explanation of the production of some forms of eczema in terms of auto-sensitiveness to cutaneous exudate, as, for instance, in two cases that he has placed on record in which an erythemato-urticarial eruption appeared nine days after trauma to a limb in which no abrasion of the skin occurred. It is possible that the elucidation of arthropathia psoriatica may ultimately be found along these lines.

Brief notes of two similar cases that have come under our observation are recorded, since they illustrate several features described in more detail in the first case.

Case II. M. P., female, aged 32, school teacher, single. This patient was seen in consultation on account of chronic and recurrent arthritis chiefly affecting the knee-joints.

The first joint trouble occurred in the spring of 1901, affecting one knee only at first, and later involving both knees. The swelling was periodical; it caused lameness, but seldom made walking impossible. Arsenic was prescribed, and after three to four months the knees became normal. Psoriasis first appeared on the scalp about a year previously. It has not disappeared since, but has always been worse at the time that the knee-swellings have occurred.

There was no return of the joint trouble until 1906. During the preceding years she had been leading a very strenuous life, working for a degree and then training for teaching. One day in London, after five days' sight-seeing, one knee began to swell, and, in the patient's words, 'I always connect it [the swelling of the knee] with an accident that occurred some weeks earlier. I fell down and

grazed one knee, and, though the graze was not serious, it would not heal for some time, and my knee felt stiff and uncomfortable. This was the first knee to be affected. After a time the other knee began to swell at regular intervals; at first the rise and fall of the swelling would cover a period of three days, and the knee would remain normal for about the same time, but these periods varied slightly—the time of the swelling lengthening out when more severe—so that if the swelling began on a Monday it was not possible to say with any certainty that it would begin again in the same knee on the following Sunday or Monday.' During the following winter, spent in Egypt, the joint trouble gradually subsided and, except for one slight relapse and some general stiffness in the joints, the patient remained in good health until the summer of 1908, when she had a slight return of periodical knee-swelling extending over three weeks. It recurred in the following summer and gradually increased, so that she had to give up work at Easter 1910. In September the swellings gradually became less severe and disappeared. Apart from a little stiffness in the knees, which did not prevent active exercise, recovery was complete.

In the winter and spring of 1911–12 she complained of pain in the right shoulder and swelling of the right sterno-clavicular joint; the pain was worse at night and after exertion. Again, in the summer of 1912, the knee trouble returned slightly and the periodical knee attacks alternated with swelling of the ankles. Since that time the patient had not been free from arthritis; the periodicity had not been obvious, but the affection had spread to other joints. In the spring of 1914 the following joints were involved: both knees, ankles, and shoulders, the neck, right sterno-clavicular joint, and carpo-metacarpal joint of the right thumb. In this note there is no record of the menstrual history.

The case is in many respects comparable to that of the first patient. Thus it is a case of psoriasis, with recurrent attacks of polyarthritis, in which the psoriasis is aggravated when the joint affection is more pronounced. The patient attributed the onset of one attack to an injury of the knee, and the most interesting feature is the occurrence of intermittent hydrarthrosis in the knee-joints throughout the earlier history of the case.

Case III. R. W., female, aged 34, dress-cutter, single, was admitted to President Ward, St. Bartholomew's Hospital, July 30, 1919, complaining of psoriasis and polyarthritis.

She was quite well until six years ago, when she first began to suffer from a scaly eruption on the knees and elbows, which appeared every spring and autumn, and cleared completely in the summer and winter. There was no joint trouble at this time.

Four and a half years ago she began to have pains in the joints; there was no swelling. The pains came and went with the psoriasis, and were preceded by the psoriasis by an interval of 4–6 weeks.

The attack on account of which the patient was admitted was of unusual severity. It began in October 1918 with the appearance of psoriasis, and there was swelling of the joints for the first time in the following December. There was sudden onset of pain and swelling in both knee-joints, followed by swelling of the finger-joints. The skin of the hands and the nails were affected for the first time. The condition gradually progressed up to the time of admission, when the psoriasis was very extensive and several joints were affected with arthritis, namely, both knees, both ankles, and many of the finger-joints. Dr. Adamson diagnosed the skin condition as psoriasis vulgaris, and further reported that the lesions about the wrists and feet bore a close resemblance to gonorrhoeal hyperkeratosis (18). Examination of the patient, of fluid removed from a knee-joint, examination of the blood, and search for focal infection threw no new light on the case. The patient was discharged from hospital on January 7, 1920, by which date the psoriasis had disappeared and the arthritis was much improved. Recovery followed, and she kept well until January 15, 1923, when the psoriasis

returned, and at the same time a little pain in the right ankle and third left metatarso-phalangeal joint. This attack subsided rapidly, and in April the patient was practically recovered.

The same menstrual irregularity was observed in this patient as in Case I; thus during the whole time of her treatment in hospital there was amenorrhoea, and during the previous attacks the periods were scanty, lasted only two days, and occurred every fourteen days instead of every twenty-eight days. The patient attributed the origin of the first attack to nervous shock due to the death of a close friend; she attributed the recent attack to the shock of finding her father lying unconscious on the floor of his room. Apart from the fact that the patient states that her relations are excitable in temperament, there is no family history of nervous instability.

This case closely resembles Case I in the recurrence of psoriasis, arthritis, and menstrual irregularity as a clinical syndrome. It only differs from that case in the absence of a history of physical trauma and the absence of intermittent hydrarthrosis. It has not, up to date, been of the same degree of severity, and there is not as yet any appreciable damage to the joints.

Conclusion.

Any one who has the opportunity of watching such cases of psoriasis with lesions of joints, which are not very rare, can hardly fail to come to the conclusion that the two complaints are intimately connected, and due to a common cause. In their clinical features the articular lesions are very similar to those of chronic infective forms of arthritis, but the remarkable recovery which takes place when the psoriasis clears up is unlike anything seen in the cases ordinarily classed under the name of rheumatoid arthritis, and is only approached in severe cases of dysenteric arthritis. In one of our cases here described, a patient who appeared to be hopelessly crippled was able to resume her work as a song and dance artiste. To all appearance both the cutaneous and articular lesions are very amenable to treatment with arsenic, which also is the drug of chief value in cases of intermittent hydrarthrosis.

It must be borne in mind that two of the cases here recorded are quite peculiar in the intermittent hydrarthrosis seen in some of the joints. We have never met with this phenomenon in other cases of the kind, but it is well known that whereas intermittent hydrarthrosis is sometimes primary, it may occur as a secondary phenomenon in cases of arthritis of various kinds.

It seems probable that psoriasis with arthritis is a definite clinical entity, and that neither lesion can be regarded as a mere complication of the other. From this standpoint they may be regarded as comparable with the articular and cardiac lesions of rheumatic fever, or with the parotid, orchitic, and pancreatic manifestations of mumps. As not all cases with rheumatic fever develop cardiac affections, and pancreatic affection is rare in mumps, so the great majority of sufferers from psoriasis have no trouble in their joints.

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THE OPERATION OF CARDIOLYSIS

WITH A DESCRIPTION OF TWO FRESH CASES, AND AN ANALYSIS OF THE LITERATURE

By GEOFFREY BOURNE

Introduction.

DR. SAMUEL GEE, in his book on *Auscultation and Percussion* (1), says: 'There are no certain signs of adherent pericardium. When the pericardium adheres not only to the heart within, but also to the walls of the chest in front, and to the spinal column behind, the following signs may be present.' There then follows a description of physical signs.

It is for the embarrassment to the heart caused by such thoracic adhesions that the operation of cardiolysis—'freeing of the heart'—has been devised, and it is to the condition in which such adhesions between the heart and its surroundings occur that the term 'adherent pericardium' is taken to refer in the following account.

Delorme (2) and his school investigated the possibility of actually freeing the heart from the adhesions binding it to surrounding structures by division. Pericardiotomy was performed. Delorme's operation is therefore very infrequently performed owing to recurrence of adhesions.

Brauer (3), in 1902, suggested that if the structures to which the heart was anchored and against which it pulled were rendered movable and yielding, no further reason for cardiac embarrassment would remain. He suggested the removal of portions of those ribs that adhered to the pericardium and to the heart. Brauer's operation avoids any attempt at freeing adhesions; it renders their effect nugatory.

The causes of adherent pericardium are acute rheumatism and tuberculosis, the former being responsible for the large majority. Of the twenty-five cases described in this paper two were tuberculous, two were possibly so, one was doubtful, and the remainder rheumatic.

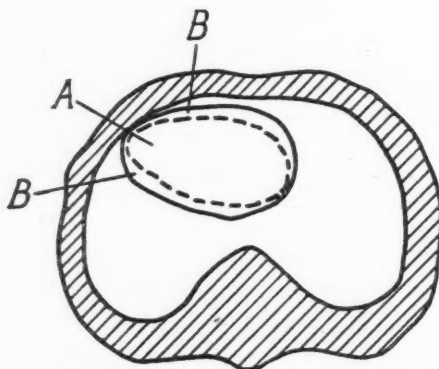
Diagnosis.

Perhaps the single sign that is most suggestive of adherent pericardium, and the one clue that should always stimulate search for others, is considerable ventricular hypertrophy not readily explainable by aortic regurgitation or a

raised tension. Other signs are: *On inspection*—(1) Periapical systolic recession; (2) Broadbent's sign; (3) inspiratory filling of the neck veins (Wenckebach). *On palpation*—(1) Fixation of the apex-beat;¹ (2) diastolic shock; (3) pulsus paradoxus.

Two instrumental means of diagnosis are useful: (1) *The electrocardiograph*. Absence of change in the shape of the electrocardiographic curves when the patient lies in the three positions—dorsal, right and left lateral—is good evidence of fixation of the position of the heart. Normally this rolling from side to side will in most cases cause slight but definite variation in the size of the ventricular complexes. (2) *The radiograph*. Elsworth Smith (4) mentions systolic traction upon the diaphragm, as seen upon the screen, as a sign of adhesion between this organ and the heart. In his case the sign was present before and absent after operation.

The mechanism by which some of these signs are produced is worth consideration, for an understanding of it will reveal the reasonableness of urging



Cross-section of thoracic wall and of heart. (Dotted line = size during systole.)

operation in the earlier cases of adherent pericardium at that stage when a good recovery is still possible.

Periapical recession. During systole the apex is thrust against the chest-wall, but all the periapical area of the heart's surface is drawn, by systolic shrinkage, away from this. So, in the diagram, adhesions at A will cause no cardiac inconvenience, but those at B will prevent efficient systole and incidentally cause the 'systolic recession' typical of the condition. It will be noted that this recession is, strictly speaking, not apical but periapical. It is almost invariably present.

Diastolic shock. The systolic contraction causes tension upon the adhesions and some yielding and in-drawing of surrounding adherent structures towards the heart. When systole ends, the pull exerted by these comes abruptly into

¹ It is almost needless to say that the sense of touch alone, the eyes being closed or averted, must be used.

play. The intracardiac negative pressure is immediately at its maximum and the shock of the inflowing blood is felt at the praecordium. The influx of the blood into a chamber in which the pressure is mechanically abnormally low produces a mild 'water-hammer' effect. Diastolic shock appears to be a sign of extensive adhesions. It is not necessarily present in the earlier cases.

Inspiratory filling of the neck veins. Pulsus paradoxus. During inspiration Keith (5) has shown that the lung roots normally descend with inspiration, 'carrying their pump with them'. When the heart is anchored above to the ribs this descent is hindered; the heart in fact becomes simultaneously pulled upon from above and below.

The position of the adhesions in any individual case will determine the presence of the physical signs.

Should traction be exerted around the opening of the superior or inferior cava, inspiratory filling of the neck veins or inspiratory diminution of inflow into the heart, and thus of output from it (i.e. pulsus paradoxus), will result.

These two signs are thus probably manifestations of incomplete auricular filling.

Wenckebach (6) suggests a similar solution to explain the frequent liver enlargement and tenderness that are so often found in the later stages of the condition, even apart from swelling of the legs and feet. He believes it possible that abnormal inspiratory traction upon the crura of the diaphragm compresses the blood in the upper part of the inferior cava and thus leads to undue distension of the hepatic veins and ultimately causes swelling of the liver.

History.

Three points are worthy of emphasis as being frequent in the histories of patients suffering from adherent pericardium.

1. *A history of acute pericarditis.* This condition may have been evident at the time, but careful perusal of reported cases will discover a number who date their history of articular pains or their symptoms of heart failure from an attack of 'pleurisy'. This fact is so striking that it throws suspicion upon the correctness of the original diagnosis. Even apart from this the pleurisy and chest pain so frequent in cases of rheumatic pericarditis may well account for many of the diagnoses of 'pleurisy'.

It is suggested that these were from the first cases of rheumatic pericarditis. The attacks of 'pleurisy' were often left-sided. Schlayer's (7) case giving this history had at the autopsy mitral stenosis indicating a definite rheumatic history.

2. *A history of heart failure of a special type.* Patients suffering from adherent pericardium are suffering from a mechanical embarrassment to a moderately healthy myocardium rather than from a severe degree of myocardial insufficiency. When the work of the heart is increased this handicap appears to come more abruptly into play, so that whereas below a certain level of effort

signs of heart failure are absent, when the heart's work is raised above this line they appear in rather an abrupt manner.

Clinically such patients may be quite free from signs or symptoms of heart failure when abed, but when up and about they rapidly manifest both. This is the most typical point in the histories of such cases.

3. In cases of hypertrophy or of heart failure in whom there is found no sufficient cause, adherent pericardium may be the explanation.

The Operation.

Cardiolysis was first suggested by Brauer (3) in 1902 and performed by Petersen.

The chief operative manipulation was the removal of portions of those ribs to which the pericardium was adherent. For the exact operative technique reference must be made to text-books of surgery. Good accounts are also provided in the articles of Melchior (8) and Schlayer (7). Briefly, a horseshoe-shaped incision is made with the curve downward, a flap of the soft tissue is turned up, and portions of the third, fourth, and fifth costal arches are removed with their anterior periosteum. The posterior periosteum is left, for the risk of new bone formation is slight; moreover, an attempt to strip it from the firm fibrous adhesions that lie behind may result in danger to the pleura and even to the cardiac muscle itself. Should new bone form, it is likely to be moulded, in process of its formation, by the movements of the heart. Thus the new ribs by their position will not oppose the cardiac movements as the original ones did.

Dangers of the operation. The chief dangers of the operation are those due to the firm fibrous adhesion between the chest-wall and the neighbouring tissues. A pneumothorax, in spite of considerable care, is of fairly frequent occurrence (9, 10, 11). Damage to the heart-muscle itself is possible.

A lesser danger is the risk of rekindling the local inflammatory condition by mechanical interference. A prophylactic course of sodium salicylate would seem to be the best means of countering this in the rheumatic cases. There is no record of local acute inflammation being stirred up in those due to tuberculosis. There is no record of death during the anaesthetic.

So far from the operation causing inconvenience to the cardiac function, several observers comment on the improvement in cardiac contraction and output during its course. Resection of a rib is so frequently performed during the course of an acute pneumococcal infection, that there would seem to be no good reason for expecting an added risk when the disease happens to be rheumatic.

Indications for operation. In considering the advisability of performing cardiolysis in a case of adherent pericardium, it should be remembered that such cases are the result of acute rheumatism.² Furthermore, an attack of

² Newton Pitt (*Practitioner*, lxxxix. 171) states that in a long series of post-mortems, 400 cases of pericardial adhesion were rheumatic, 23 were tuberculous, and 42 were due to malignant disease.

rheumatic pericarditis that has produced considerable adhesion of the pericardium has been a severe one.

Acute rheumatism is a progressive disease, and the rapidity of its progress is often in proportion to the severity of its manifestations. Thus, whatever treatment is undertaken, a case of rheumatic pericarditis with adhesions will never suggest an optimistic prognosis. Cardiolysis may have an effect in some cases of improving the prognosis, but it must be remembered that no mechanical shift, however ingenious, can hope to arrest the progress of a scattered and deep-seated infection.

But although the primary problem is undoubtedly to discover and to remove the cause of acute rheumatism, any measure that can definitely improve the clinical condition should be taken.

That cardiolysis will improve cardiac efficiency in certain cases is without doubt. This improvement in the circulation must be of benefit for three reasons:

The blood-supply to all the organs of the body is improved.

The patient's powers of healthy exercise are increased.

The coronary circulation, and therefore presumably the cardiac nutrition, is benefited.

It is conceivable that such effects may indirectly have some favourable result on the causative disease itself.

Briefly, therefore, it may be stated that cardiolysis is indicated in cases of adherent pericardium where the rheumatic infection seems arrested, latent, or only slowly progressive, and where signs or symptoms of heart failure are present.

The indication that is usually given for cardiolysis is 'heart failure of such a degree that it is latent during rest in bed and present when the patient is up'—such heart failure being due, of course, to adherent pericardium. Poynton (12) says that the cases in which the measure is indicated are those in which the heart is 'just adequate for active life'. Hirschfelder (13) states: 'As regards indications for cardiolysis, it would appear that, since the adherent pericardium cannot otherwise be relieved, this operation is worthy of a trial whenever symptoms of cardiac weakness occur and recur in a patient with well-marked adhesions to the chest-wall (tugging in of the lower ribs, fixation of the left border of cardiac dullness on inspiration, immobility of the apex).'

This type of history is certainly that which is most frequent in cases of heart failure due to adherent pericardium, and it is rather a point of diagnosis than a specific indication for operation. There seems to be no adequate or reasonable explanation for restricting the operation to cases which give such a history. Indeed, such restriction actually tends to limit the measure to those cases who are least likely to obtain lasting benefit from it. There are many degrees of heart failure, slight and severe: *if adherent pericardium be seriously considered as a factor in their production, cardiolysis should be performed irrespective of the degree or type of failure.*

Contra-indications. The chief contra-indication to the operation is the presence of some severe progressive rheumatic lesion, such as advanced mitral stenosis.

Brauer (3) quotes mitral stenosis, and Hirschfelder (13) childhood, as factors that should weigh against a decision to operate. If the mitral stenosis is not advanced, and not obviously rapidly progressive, it seems to present no cogent objection to the operation. Childhood seems an objection of even less weight: lack of years is not advanced as an argument against resection of a rib for empyema. Another theoretical contra-indication might be auricular fibrillation. That it would be unsound to make that irregularity a sole reason against the performance of cardiolysis is suggested by Brauer's first case. The patient was a man with 'adherent pericardium, broken compensation, ascites, and oedema, and an irregular pulse'. After the operation he lost all his signs of heart failure and returned to work; *his pulse, however, remained irregular.*

Moreover, of the twenty-five cases hereafter described, nine were fibrillating; so far from being handicapped by the irregularity, most of these patients responded extremely well to the operation.

Cases.

The following two cases had suffered from adherent pericardium due to rheumatic infection: both were patients at the East London Hospital for Children. The operation was performed in either case by Mr. Joseph Adams.

Case A. Male aged 9 years. Seen first on September 15, 1921, he was suffering from dyspnoea on walking on the flat. There was no past history of a single severe attack of acute rheumatism, but four years previously his mother was told by a doctor that he had 'heart disease'. He was pale, undersized, lethargic, and easily made short of breath by slight exercise.

Heart. Visible pulsation was evident in the third, fourth, and fifth spaces. Systolic recession was present around the apex-beat; this latter was $3\frac{1}{2}$ inches from the mid-line in the fifth space, and remained fixed in position on movement. A systolic murmur was present, loudest at the apex-beat. Epigastric systolic recession was present. Broadbent's sign was not present. There was no pulsus paradoxus, and no diastolic shock.

X-ray. When screened the heart seemed large, and fixed, on the patient being rolled from side to side. The plates showed that, in addition, the whole heart was drawn somewhat to the left side. A diagnosis of rheumatic carditis with adherent pericardium and mitral disease was made.

On October 20, 1921, he was admitted, and as he showed no signs of active infection, Mr. Adams was asked to perform cardiolysis. This was done on November 3. The chief point in connexion with the operation was that, owing to the density of adhesions between the fifth rib and the surrounding parts, removal of the bone caused a slight pleural tear resulting in a partial pneumothorax. This cleared up in a week, and the patient made an uneventful recovery from the operation.

Seen on January 11, 1922, he seemed healthy. He had had no recurrence of acute rheumatism. There was no dyspnoea on walking; moreover, he could run upstairs without getting short of breath. He played freely with other children and went to school. He had since successfully surmounted an attack of broncho-pneumonia.

Heart. The cardiac murmurs were unchanged. The apex-beat was $3\frac{1}{2}$ inches from the mid-line, and moved about $\frac{1}{2}$ inch on rolling from side to side. There was a well-marked systolic retraction of the whole soft praecordium. There was as yet no re-formation of the ribs, as shown radiographically.

On June 7, 1923, the apex-beat was $3\frac{1}{2}$ inches from the mid-line in the fifth interspace. The systolic thrust was more forcible and an aortic regurgitant murmur was audible in the second space on the left side. He had no symptoms of heart failure.

Case B. Male aged 10 years. There was no history of rheumatic infection. He was admitted on October 29, 1920, suffering from acute rheumatic pericarditis. The attack was a severe one; pyrexia to 102 was present for seventeen days, the pulse-rate was at first 160, friction was present over the whole praecordium, the greater part of the left lower lobe was collapsed.

After the attack had subsided, it was noticed that the apex-beat was fixed in position, and that there was considerable intercostal and epigastric systolic recession. Double mitral murmurs were present, the apex-beat was 5 inches from the mid-line in the fifth space. On February 19, 1921, 123 days from his first admission, cardiolysis was performed by Mr. Adams.

Directly after the operation he had fever for ten days, and his pulse-rate was raised for about a fortnight. On March 7 he was up walking, the wound was healed, and the apex-beat was movable $\frac{1}{2}$ inch on either side of its central position: it was now $4\frac{1}{2}$ inches from the mid-line. He was seen in September 1921, and was found to have been playing football in the street, his mother pleading inability to control him.

On November 23, 1921, he had a short, rather severe attack of broncho-pneumonia, from which he recovered in three weeks. There was no cardiac disability afterwards.

On October 5, 1922, he was complaining of pains in the joints. These were controlled by salicylates.

His pulse-rate standing was 84, and there was no change in his cardiac condition. He was apt to get short of breath occasionally, but was otherwise healthy (January 11, 1922).

On June 7, 1923, the cardiac condition was unchanged. He was still free from symptoms of heart failure, except occasional dyspnoea on considerable exertion.

These two cases showed adherent pericardium, both clinically and at the operation. The signs and symptoms were of an early rather than of an advanced lesion. The operation was well borne and completely successful in either case.

Abstract of 23 Cases from the Literature.

Brauer, *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1903, xxxii. 80.

(1) *Male aged 50.* Before operation he had been bed-ridden with heart failure. He had oedema, ascites, enlarged liver, and an irregular heart rhythm.

A year afterwards he was relatively vigorous and active and able to work in a motor factory. Four years after he was still in good health.

(2) *Male aged 25.* Symptoms of heart failure were present before the operation. These were relieved by it. He died ten months afterwards of broncho-pneumonia.

(3) *Male aged 16.* Cyanosis considerably relieved by the operation. Rheumatic history.

Meyer-Westfeld, *Munch. med. Wchnschr.*, 1905, lii. 1930.

(4) *Male aged 24.* There is a history suggesting rheumatic pericarditis at the age of 18, followed by oedema of feet and symptoms of heart failure at a year's interval. Before the operation he had a dilated heart, double mitral murmurs, diastolic collapse of neck veins, diastolic shock. The abdominal cavity contained more than three litres of fluid, the liver and spleen were enlarged.

After cardiolytic the dyspnoea and cyanosis disappeared, no further ascites was noticed, the liver became rapidly smaller. He was discharged from hospital fit for light work.

Unger, *Therap. d. Gegenw.*, 1905, xli. 10.

(5) The adherent pericardium in this patient (an adult) was due probably to tuberculous infection, as death was due to generalized tuberculosis and calcareous plaques were present in the pericardium at the autopsy.

Cardiolytic had been performed 2½ years before death and was followed by a relief of ascites, oedema, and other signs of heart failure. The liver was cirrhotic at the time of death.

Danielsen, *Beitr. z. klin. Chir.*, 1906, li. 131.

(6) *Male aged 20.* There was a history of articular rheumatism for six years and pulmonary catarrh for ten. Cyanosis, diastolic collapse of veins, fixation of the apex-beat, diastolic shock, great pulse irregularity, were all present. The liver was enlarged and ascites was present. Nine months after the operation his symptoms of heart failure had disappeared, he returned to his trade as a butcher. His apex-beat was then movable.

Unger, *Deutsch. med. Wchnschr.*, 1907, xxxiii. 1883.

(7) *Female aged 42.* There was no history of articular rheumatism, but she had been under her doctor's observation for a cardiac defect for some years. For three years she had had signs of slight heart failure. A few months before admission she suffered a sudden loss of compensation. When seen she had much oedema of the feet and legs, congestion at both bases, enlarged hard liver, ascites, albuminuria. The pulse tracing showed auricular fibrillation, the onset of which may have been the exciting cause of her severe symptoms.

Drug treatment caused a transitory improvement. A fortnight after cardiolytic she had no ascites or oedema and was able to be on her feet without signs of failure. Three months after she was taking daily walks of from three to four miles. Two years after she was still well.

Wenckebach, *Brit. Med. Journ.*, 1907, Jan. 12.

(8) *Male aged 14.* During the summer of 1903 he had an attack of 'pleurisy', in 1904 he had pericarditis. This was followed by dyspnoea, general anasarca, and enlargement of the liver. The heart showed systolic retraction and the pulse was paradoxical in type.

A year after the attack of pleurisy cardiolytic was performed. Eighteen months after, daily pyrexia was present and there was no great improvement visible. Wenckebach hints at a possible tuberculous cause, and states that the operation saved the patient's life and made it bearable.

Urban, *Wien. med. Wchnschr.*, 1908, lviii. 395.

(9) *Male aged 22.* He suffered from articular rheumatism at 16 years of age. Symptoms of heart failure appeared soon after. At 20 years of age oedema of the feet and legs appeared. On examination, cyanosis, oedema of legs, and ascites were present. Systolic recession and diastolic shock, diastolic collapse of veins, irregularity of the pulse, and enlargement of the liver were all observed. Drug treatment allayed the symptoms in bed only.

Cardiolytic was performed. Pulse regularity appeared, ascites and oedema

had gone, the heart shadow radiographically was 3 cm. less in diameter. Tubercle bacilli were found in his sputum three months after the operation although his heart condition remained much improved.

Poynton and Trotter, *Proc. Roy. Soc. Med.*, June 1909.

(10) *Male aged 16.* He was admitted with oedema of legs and feet of three months' duration. The onset of his symptoms of heart failure had been gradual. Examination showed cyanosis, fixation of the apex-beat, systolic retraction, and slight hepatic and splenic enlargement. Rest caused only temporary improvement.

Cardiolysis was performed; eight months after the writers said, 'At the present time we believe that the operation has been justified by the result, even if the improvement goes no farther.' He had lost all his oedema except slight pitting about the ankles, and could undertake half an hour's walk without fatigue. His condition appears to have been rheumatic in origin.

Venus, *Wien. klin. Wchnschr.*, 1911, xxiii. 592.

Briefly refers to twenty cases. There was no operative fatality among them. He gives a full dissertation upon operative technique.

Schlayer, *Munch. med. Wchnschr.*, 1910, lviii. 729.

(11) *Case IX. A man aged 32.* He had an attack of pleurisy at the age of 20. This left him with slight shortness of breath and palpitation. A few months before admission cyanosis and abdominal enlargement appeared. On examination he showed cyanosis, overfilled neck veins, and dyspnoea but no oedema, systolic recession, diastolic shock and enlargement of the heart, ascites, and enlarged liver.

Cardiolysis was performed. He died suddenly twelve hours after the operation.

The post-mortem showed complete intrapericardial adhesion, mitral stenosis and insufficiency, and an enlarged liver. This case thus probably started as a rheumatic pericarditis.

(12) Schlayer's 'Case II.'

A man aged 49, who had had seven attacks of multiple polyarthritis, in the second of which his heart was affected, was found on examination to have cardiac enlargement, diastolic shock, enlargement of the liver, and ascites.

Cardiolysis was performed. After it he made no definite improvement, dying two years later. His lengthy rheumatic history seems to indicate that severe rheumatic myocarditis may have been present. It is unlikely that such a case would benefit much from any measure.

(13) Schlayer's 'Case VII.'

A man aged 19 had had an attack of 'pleurisy' at the age of 7; he later developed ascites and oedema of the feet; dyspnoea also was present. These symptoms lasted for a period of eight years, being improved temporarily by hospital treatment.

On examination he showed cyanosis, dyspnoea, oedema of both legs, distension of neck and arm veins; the heart's impulse was weak, diastolic shock was present; ascites and enlarged liver were present.

Cardiolysis was performed. Though the operation was at first followed by fever and an active pleurisy for a period of six months, all oedema and ascites disappeared. Ultimately the signs and symptoms recurred and proved fatal.

Simon, *Brit. Med. Journ.*, 1912, 1649.

(14) *A male aged 15* had had an attack of rheumatic pericarditis at the age of 12. Since then he suffered from a gradually increasing degree of heart failure.

He was admitted with oedema of feet and legs, ascites, and orthopnoea. He was found to have a mitral lesion. His pulse was regular. Adherent pericardium was diagnosed.

Cardiolysis produced loss of signs and symptoms of heart failure for five months. During that period, however, he appears to have developed auricular fibrillation, and at the end of it the heart failure recurred and proved fatal after a further five months.

Post-mortem examination showed 'universal' thoracic adhesions, the heart being adherent to the chest-wall, diaphragm, and the other adjacent mediastinal structures.

Summer's Case I. *J. Am. Med. Sci.*, June 1913.

(15) *A male aged 29* gave a three years' history of progressive heart failure. The only definite previous illness had been diphtheria and paralysis at the age of 11.

On examination he showed orthopnoea and dyspnoea, oedema of feet and legs, ascites. Mitral regurgitation and auricular fibrillation were present. Fixation of the apex-beat, diastolic shock, and a positive Broadbent's sign were found.

Cardiolysis was performed. The signs and symptoms of heart failure were abolished for four years, the patient returning to work. Death from heart failure occurred $4\frac{1}{2}$ years afterwards. Post-mortem examination showed mediastinitis, probably rheumatic.

Summer's Case II.

(16) *A woman aged 23* had for four years suffered from dyspnoea, praecordial pain, and latterly from oedema of the feet and legs. She had had acute rheumatism.

On examination oedema of legs and feet, ascites, a positive Broadbent's sign, fixed apex-beat, systolic recession, enlargement of the liver and spleen, were all found.

After cardiolysis there was temporary improvement, the patient being able to drive a car. Nine months after, however, she died.

Post-mortem examination showed a heart almost filling the left side of the chest and a greatly enlarged liver showing Pick's cirrhosis.

Nové-Josserand et Péhu, *Soc. Méd. des Hôp.*, 1914, 1481.

(17) *A girl aged 7* who had had chorea twice developed a mediastino-pericarditis whilst under observation. She had a systolic mitral murmur. The feet and legs became oedematous and ascites appeared. After cardiolysis she improved markedly, losing her ascites and oedema.

Courmont-Gardère et Arnaud, *Soc. Méd. des Hôp.*, 1914, 195.

(18) *A woman aged 42* had what was diagnosed as a tuberculous mediastino-pericarditis. Cardiolysis much improved her condition for three months, relieving her of ascites and dyspnoea. She died later of acute tuberculosis.

Hirschfelder's Case. *Disease of Heart and Aorta*, p. 618.

(19) *A man aged 23* was found to have dyspnoea, cyanosis, oedema of the feet, enlargement of the liver, fixation of the apex-beat, systolic recession, and Broadbent's sign. He recovered from the operation and improved, but the ultimate result is not given. The pulse rhythm was irregular.

Elsworth Smith's Case I. *Med. Clin. N. America*, 1920-1.

(20) *A woman aged 41*, who had had acute rheumatism at the age of 17, had for ten years suffered from dyspnoea, palpitation, and oedema of the ankles. She had cyanosis, oedema of the feet, ascites, enlargement of the liver, and a left-sided pleural effusion; the apex-beat was fixed, systolic retraction was

present. Auricular fibrillation was proved, and she had the murmurs of aortic and mitral insufficiency.

Cardiolysis was performed, but death supervened after twenty days.

Elsworth Smith's *Case II. Med. Clin. N. America*, November 1920.

(21) *A woman aged 38* with a past history of acute rheumatism was suffering from heart failure. General anasarca was present, her abdomen having been tapped 20 times at five-week intervals. She gave the clinical and radiological signs of adherent pericardium. Auricular fibrillation was found, with a considerable pulse deficit.

Cardiolysis was performed.

Her orthopnoea disappeared, she had much less dyspnoea, the tapping was only now at intervals of twelve weeks. The apical rate was easily controlled with digitalis and the pulse deficit abolished. Radiographically the heart was smaller.

Hallopeau's *Case. Bull. et mém. Soc. Clin., Paris*, 1921, 1120.

(22) *A male aged 16* had acute articular rheumatism and pericarditis. Pericardiotomy was performed and the surface of the heart separated digitally from the parietal pleura. He made a rapid and complete recovery.

Schmeiden's *Case. Münch. med. Wchnschr.*, 1922, lxi, 177.

(23) *A male aged 46* for a year had suffered from signs of heart failure. He was found to have cyanosis, some degree of hydrothorax, ascites, oedema of feet and legs. Systolic retraction, diastolic shock, fullness of the veins, were present.

Cardiolysis was performed, the heart being found adherent. From its anterior two-thirds thickened pericardium was peeled off. He recovered from the operation, was no longer bed-ridden, and ultimately resumed his work as manager of a brewery.

It is seen that the last two cases are not strictly classifiable as being pure examples of Brauer's cardiolysis.

Deductions from a Consideration of the Recorded Cases.

Of 25 cases: 17 were rheumatic, 3 probably rheumatic in origin, 2 were tuberculous, 2 probably tuberculous, 1 indefinite as regards aetiology. 13 cases showing oedema and ascites were greatly improved by the operation for periods varying from three months to five years. 4 cases showing earlier signs of heart failure were definitely improved. 4 cases were only slightly improved; 3 had oedema of the feet and legs, 2 had ascites also. 1 case was not improved. 2 cases died, one twelve hours, one twenty days after the operation. In one case the result is not given.

Among the recorded cases 'pleurisy', pericarditis, and ascites are a triad of lesions that appear four times. The term polyserositis would appear to owe its origin in some degree to such cases. Careful consideration of the histories strongly suggests that the 'pleurisy', which in three of the four cases comes first in point of time, was not a primary pleural inflammatory condition at all, but rather was an accompaniment of the original acute pericarditis. A history of 'pleurisy' at the age of 20, which left the patient short of breath, is very suggestive of pericarditis.

In these four cases the train of events appears to have been as follows:

A first attack of acute rheumatic pericarditis occurs masquerading as 'pleurisy'; after an interval a second attack follows which is recognized as

'pericarditis'. Adhesions occur, and after a lapse of years the failing heart, helped possibly by the liver condition, produces 'ascites'.

The completed case is labelled polyserositis, and such a name falsely suggests a common pathological origin for the serous effusions.

It is not suggested that such a common origin may not in some cases exist; but the evidence in the cases here collected is against it (Cases 8, 11, 13, 20).

Conclusions.

1. The mechanical causes of the signs and symptoms of heart failure from adherent pericardium are considered. The adherent heart is a mechanically ineffective heart.

2. Adherent pericardium can be diagnosed, and should be discovered in its earlier stages.

3. Cardiolysis is an operation with a very low mortality, and one that is productive of excellent results. It is effective in severe heart failure and should logically be performed in that of a lesser degree.

4. The chief indication for the operation is heart failure of whatever degree accompanied by adherent pericardium.

5. An analysis of twenty-five cases collected from the literature has been made.

6. Two new cases are recorded of adherent pericardium and slight heart failure. They are alive and well $2\frac{1}{2}$ and 2 years after the operation.

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EXPERIMENTS ON THE AETIOLOGY OF CHRONIC INFECTION OF THE SPLEEN

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Introduction.

IN a communication to the Royal Society of Medicine in 1913 (1), and subsequently in the *Quarterly Journal of Medicine* (2), it was suggested that certain appearances in the spleen from cases of splenomegaly of obscure origin were to be interpreted as indicating an infection of that organ by a streptothrix organism, and that judging from its position in the tissue it might be the cause of the disease. Other workers whose criticisms reached the writer were not able to agree with the hypothesis, and the full proof had to be attempted, namely, the isolation of the organism in a group of cases and ascertaining their pathogenic properties (i.e. to submit them to the test of Koch's postulates). The first opportunity of doing this occurred in 1914 on the isolation of a streptothrix organism which grew well on laboratory media from a spleen kindly sent me by Mr. Harold Upcott, of Hull (3), from a patient who had suffered from repeated attacks of jaundice and what was thought to be gall-stone colic. The properties of this organism in general have been published (4), and it is the purpose of the present communication to describe more completely the effects on monkeys, which are the only animals so far used that show pathogenic effects. Guinea-pigs, rabbits, rats, and mice show no ill effects after injection.

In the present series of twelve monkeys, ten have been injected with the organism and all have shown symptoms in a varying degree (see table on p. 193). Two of the animals were kept as controls and showed no symptoms as compared with the experimental animals for several months; both of these, however, died from intercurrent disease lasting a few days.

Owing to the difficulty of obtaining animals they had to be accepted when they could be bought; hence the animals were not all under experiment at the same time. It will be evident, however, as the experiments are detailed, that the symptoms and organic changes in the injected animals are sufficiently striking to neglect any slight differences due to season or other variable conditions.

Bacteriology.

A description of the original organism was published in the Proceedings of the Pathological Society of Great Britain and Ireland (*Journal of Pathology and Bacteriology*, 1920, vol. xxii, p. 357). It is a streptothrix of the actinomyces type growing in broth in spherical fluffy snowball-like masses, and on agar in whitish circular colonies which stick to the medium and to be removed have to be dug out. Long subculture has rendered the growth after nine years very luxuriant on either of these media, and at the end of a week on an agar slope the growth has spread over the greater part of the surface as well as some distance into it. One feature this culture presented in its earlier subculture, namely, an efflorescence of a white powder on the summit of the colonies, has now disappeared; this property has been marked in the culture from monkey No. 211. Microscopically it is a streptothrix with true branching, and is Gram-negative except in the oldest parts of the fibre and in points along the fibre. The efflorescence appears as small Gram-negative coccal bodies.

The organism was detected in the culture tubes originally made from the spleen 18 days after planting, and it was thought that a like interval or thereabouts would be found in the successful results in monkeys; this, however, has not been so. In No. 200 the growth appeared only after an interval of 65 days, and four implantations into new media, though in the broth tubes long threads could be found. In the blood culture from No. 211 it appeared in 13 days. In some instances the growth has little or no power of propagating on agar media, even after prolonged subculture; the organism isolated from No. 210, typical in morphological appearances both in broth and agar, cannot be subcultured except in serum broth. No explanation of these facts can be given, but it emphasizes the difficulty and uncertainty of obtaining bacterial culture from human cases and from the organs of the animals in this series. This difficulty of isolation and fickleness of growth is a feature of actinomycotic organisms when they affect other parts of the body.

It will be seen in the table of results, p. 193, that only in three animals of one species, *Macacus sinicus*, which were all of that species used, was a positive bacterial result obtained. Of these one was obtained from the spleen (No. 200), another from a gland of the groin and from the spleen (No. 210), and the third by blood culture during life (No. 211). It is to be noted also that the growth was obtained in one out of 15 tubes in No. 200, in two out of 19 in No. 210, and in one out of 24 tubes in No. 211.

Symptoms and Physical Signs.

Ten out of twelve animals in the series received injections of a broth culture or an emulsion in saline of the original organism, either intraperitoneally or by the intravenous route. The latter method has considerable difficulties in the monkey by reason of the smallness of the veins, and as the effects were the same

by both methods the intravenous route was not used in the later injections. The effect of the injection appeared to be slight in one instance (No. 204); three injections were therefore given, and in two others, Nos. 205 and 206, two injections.

The effects in the series of animals fall into three groups:

1. The two controls (Nos. 208, 209), *Cercopithecus callitrichus*, appeared well and lively until a few days before death. The difference in their move-

No.	Species.	Incuba- tion (Days).	Symptoms.	Death after (Days).	Post-mortem.	Bacterio- logical Result.
200	<i>Macacus sinicus</i>	37	Debility, wasting, tender abdomen, enlarged spleen	194	Enlarged fibrous spleen, portal in- flammation, and liver scars	+
210	" "	19	Debility, wasting, signs of nervous disease	341	Fibrosis of spleen, portal inflamma- tion, scars of lung, granuloma of brain	+
211	" "	42	Debility, wasting, loss of power, anaemia	614	Fibrosis of spleen, portal inflamma- tion, not general, infarct of lung	+
201	<i>Macacus rhesus</i>	18	{ Debility, emaciation Oedema General tuberculosis	73	General tuberculosis	-
202	" "	9		18		
203	" "	13		47		
204	<i>Cercopithecus callitrichus</i>	97	Debility, wasting, tender abdomen, paresis of legs	575	Fibrosis of spleen, portal inflamma- tion, lung haemo- rrhages	-
205	" "	46	Debility, wasting, tender abdomen, paresis of legs, pul- monary embolism	973	Fibrosis of spleen, portal inflamma- tion, infarct and scars of lung	-
206	" "	100	Debility, tender ab- domen	252	Fibrosis of spleen, ulcers of stomach and caecum, portal inflammation, in- farcts of liver, haemorrhages in lung	-
207	" "	15	Debility, tender ab- domen, death with unconsciousness	154	Fibrosis of spleen, portal inflamma- tion	-
208	" "	Control	None	135	Hyperaemia of or- gans, no fibrosis of spleen	
209	" "	Control	None	98	Post-mortem diges- tion of stomach, no fibrosis of spleen	

ments as compared with the others was most marked. Their weight increased steadily. At no examination was any tenderness of the spleen, liver, or abdomen generally found. The spleen and kidney could frequently be felt.

2. The three injected animals of the species *Macacus rhesus* (Nos. 201, 202, 203), in which there was a gradual wasting, debility, tendency to oedema, and a poor coat. The spleen and liver enlarged as the illness progressed, and projections on its surface were marked. The appetite usually failed in the last

fortnight, differing from the next group in which it remained throughout. Pallor was noticed in one (No. 203), diarrhoea in two (Nos. 202, 203), in one of which (No. 203) ulceration of the colon was found at post-mortem. Cough was noticed in one (No. 203).

3. The third group comprises seven injected animals (Nos. 200, 204, 205, 206, 207, 210, 211) in which a gradual progressive debility showed itself. As the laboratory attendant (Mr. G. Cox) expressed it, the animals 'appeared doped'. They sat in the corner, usually the same corner, of the cage all day, seldom moving except to take food or when disturbed. Pallor of the face and gums was noticed in all instances as the disease advanced, and was specially marked in Nos. 210 and 211. The disposition did not alter except in one (No. 205) in which was noticed a period of more violent temper; it was more easily excited to wrath than the others, and at a later stage became docile and could be stroked, which previously had been unsafe. Loss of weight and emaciation was invariable, but in no case was it very marked. In the earlier part of the experiments some of the animals, under the proper conditions of feeding, showed a slight increase; but in all the animals under experiment the loss of weight was sooner or later manifest. The amount of fat in the monkey's body is very small, and therefore loss of weight cannot be so marked as in other animals that have this tissue to lose. The greatest loss was in No. 205, which fell from 3,600 to 2,430 grm., nearly one-third of its weight.

Abdominal tenderness was the most marked feature of the injected animals. It was never found in the controls, in which deep palpation could be done without any resistance. In the injected animals, however, deep palpation was impossible because of muscular rigidity; the animal blinked or winced if palpation was persisted in, and frequently the hand of the monkey would be used forcibly to remove the palpating fingers of the observer. In nearly all the monkeys before the injection careful palpation would detect the spleen and kidney, frequently also the liver, and the two former organs occasionally could be held between the fingers firmly without apparent discomfort. But any examination of this kind was obviously uncomfortable some weeks after injection. The tenderness was more marked on the left side than on the right, but from time to time it could be observed in all regions. A marked enlargement of the spleen occurred in No. 200.

The appetite never failed, bananas and apples always excited eagerness. The diet consisted of rice, milk, potatoes, and fruit. The stools were never abnormal and the absence of diarrhoea was unusual throughout so long a period of observation.

The nervous symptoms include: (1) attacks of faintness which from the increase of respirations and the post-mortem appearance of the lung may be ascribed to pulmonary embolism; (2) an epileptiform fit (207); (3) muscular weakness which is especially marked in the lower limbs, but sometimes present in the upper; (4) ataxia was noticed in Nos. 205, 210; (5) frequent yawning was noticed in Nos. 204, 205, and 211.

More complete descriptions of the nervous symptoms will be found in the description of the animals Nos. 210 and 211, which were examined by Dr. F. M. R. Walshe.

Blood Examination.

The blood counts, except in one case, No. 210, showed no anaemia; rather the red cell count showed a polycythaemia. A search through available literature failed to discover any extensive series of blood counts in individual species of monkeys that enabled any use to be made of the estimations in this series. The polycythaemia, which was in several instances over 8,000,000 red cells, was not present in the first counts, and may have had some connexion with better conditions of housing and food in the laboratory. It appeared not to correspond to the winter more than the summer, and was present in the controls as well as in the experimental animals.

No. 210 showed a chlorotic anaemia of R. B. C. 4,900,000 and Hb 56 per cent., and in this animal the haemoglobin never rose above 68 per cent., having been 60 per cent. at the beginning. An almost similar animal, No. 211, showed marked pallor in the later stages, but a haemoglobin reading which was 80 per cent. at the beginning rose to 106 per cent. after the experiment had been going on for nine months. In the absence, therefore, of an extended series of control counts no deductions can be made.

The fragility was tested from time to time in six of the experimental animals and one control. It has never been found different from the control, nor has it varied at different times. The first sign of fragility has not been above 0.48 per cent. NaCl except in No. 204 fifty-seven days before death, when it appeared at 0.54 per cent. NaCl. Full haemolysis has been present at 0.32 per cent.

The possibility of blood cultures being successful suggested itself in view of the presence of pulmonary embolism, the evidence for which is elsewhere discussed. Only two animals, Nos. 205 and 211, were used, and each had four cultures, with negative results except in one, No. 211, in which, after thirteen days, one of a series of six tubes grew an organism with the typical features of that used for injection.

Morbid Anatomy.

The appearance of the organs in this series of twelve animals falls into three groups, which correspond to those mentioned under Symptoms.

(a) Two animals, *Cercopithecus callitrichus* (Nos. 208 and 209), which were kept as controls, in which no chronic lesion could be detected. No lesions or scar could be found other than the acute post-mortem digestion of the stomach in one animal. In neither animal was the cause of death ascertained.

(b) Three animals, *Macacus rhesus*, Nos. 201, 202, 203, with lesions of acute disseminated caseous tuberculosis. In these the cause of death was obviously tuberculosis.

It is a matter of common knowledge in this country amongst those who have

to deal with monkeys that the *rhesus* frequently dies from this cause, and that death is often preceded by diarrhoea corresponding to lesions in the gut. In only one of these animals was an ulcer found in this situation, and it was not possible to ascertain whether this existed before the experiment. None of the animals, however, was in poor health at the beginning of the experiment, and it is clear from the short intervals, 18, 9, and 13 days respectively, between the injection and the first symptom, that the injection of the streptothrix was presumably the determining factor. The animals were all given milk in their diet, and this may have contained tubercle bacilli. Other animals of the same species, however, had been under experiment under exactly similar conditions of housing and diet with no ill effects.

(c) The third group comprises three of the species *Macacus sinicus* (bonnet) and four of *Cercopithecus callitrichus*. All of these animals showed lesions in various organs.

The *spleen* was markedly enlarged in one (No. 200); in the others it was small, and in three it was much shrunken. In all there was evidence of increased fibrosis and atrophy of the Malpighian bodies. Endophlebitis was also present in varying amount in all. In some there were patches indicating a chronic inflammatory process, aggregation of leucocytes, klastocytes, and fibroblasts. These areas showed no characteristic features by which they might be recognized elsewhere. In no spleen was there found any of the haemorrhagic scars so frequently seen in chronic splenic inflammation in man, but some collection of cells containing pigment was occasionally seen in close relation with trabeculae.

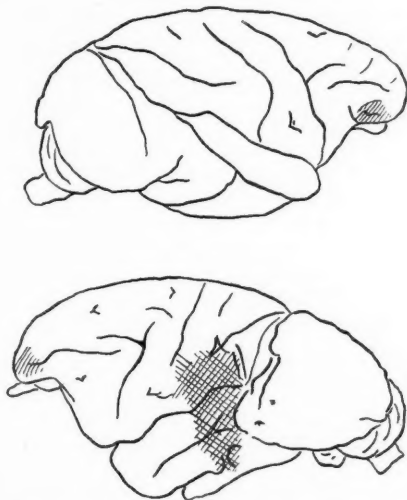
The *liver* in two animals (Nos. 200 and 206) showed infarcts, in one (No. 200) scars were also present; in other three (Nos. 205, 210, 211) infarcts were not found, though in one there was a healed scar (No. 204). In No. 200 a fibrinous mass, probably an embolus, was found attached to the wall of a branch of the portal vein at one spot. In all there was portal inflammation, a slight infiltration of the walls of the portal vein and Glisson's capsule. In No. 210 there was a narrowing of the arterial lumina and periarterial thickening. As to the liver parenchyma, all showed fatty changes, occasionally very intense in patches.

Changes in the *lung* were present in all except two (Nos. 200 and 207); in two (Nos. 206 and 211) there were infarcts, and this was confirmed by the microscope; in one of these, indeed, the fibrinous embolus blocking the pulmonary artery was quite evident. In one (No. 204) there was acute pneumonia; in the others the changes seen were petechial haemorrhages and healed scars. Under the microscope the haemorrhages were always near an artery which showed end-arterial changes and narrowing of its lumen. The scars were evident to the naked eye on the surface, especially of No. 205, and were also marked under the microscope; they were sometimes linear, stretching out into the lung from a branch of the pulmonary artery. No changes of the nature of broncho-pneumonia, except in one, were detected; in fact the mucous membrane of the bronchioles, except near the changes just described, was normal. The changes as described would imply a process of embolism; the source of such embolism,

however, was not discovered either in the right heart or origins of the venous system.

The *stomach*, normal in three, was found to contain recent haemorrhagic ulcers in two others, and in one of these there were ulcers in the small intestine with melaena; a small mesenteric haemorrhage was also present. Sections of the ulcers themselves failed to give any evidence of their origin, but in conjunction with the changes in the splenic veins (endophlebitis) it is clearly probable that a process of portal embolism in some venous branches of the vasa brevia may be present. This observation would appear to throw light on the tendency to haemorrhage seen in human splenic anaemia.

The *kidney* in all instances but two has been without changes; in these, however, there were healed scars (Nos. 205 and 210).



Right and left aspects of the brain of monkey No. 210, showing the site of the lesion in the left parietal and temporal lobes on either side of the termination of the Sylvian fissure.

The *brain* showed gross changes in one only (No. 210). In this, on the left side of the hemisphere, there was an extensive slightly-depressed scar (see figure above) where the convolutions had been shrunken and lost their opacity. Several small arteries were blocked by endarteritis, but, apart from the intracellular bodies described later, no evidence of the organism was discovered. The changes appeared to be of the nature of a cerebral softening, atrophy, and scarring. In one other animal recent haemorrhage was found over the pons.

Histology. In all the sections which showed evidence of inflammation, more especially in the spleen, liver, lung, and the brain lesion of No. 210, special search has been made for the organisms of the streptothrix type. Only by extremely careful and prolonged search under the highest powers can anything be found that resembles a streptothrix. Various stains have been used for this purpose. They may be seen in the haematoxylin and eosin preparations, also by the method

known as Wheal and Chown, and by cresylecht violet. They appear as small sinuous threads, sometimes with a free segment at the end; more commonly short bacilli are to be found. The difficulty of making sure that these elements are not tissue threads, drawn-out leucocytic nuclei, or, in the case of bacilli, accidental, is one which it has not been possible to overcome by histological or staining methods; and no evidence of the infecting agent on this method can be claimed. Further details of minute structure would only serve to confirm the evidence, already sufficient, for the presence of chronic inflammation.

Abbreviated Notes of Experiments.

Monkey No. 200. A full-grown bonnet monkey, *Macacus sinicus*, which had been under observation in this country for over two years. It was tame and well nourished. Nothing abnormal could be felt in the abdomen, and neither spleen nor liver could be felt.

On January 8, 1919, 2 c.c. of a 24-hour broth culture of Upcott's organism were injected intraperitoneally. There was no immediate effect, and nothing in the days immediately following except slight diarrhoea after three days. Thirty-seven days after the injections the liver could be felt and the spleen was enlarged and tender. From that time until July 21, 1919, 194 days after the injections, the animal's condition deteriorated. The liver and spleen could usually be felt, and the spleen especially was tender and enlarged, until it extended downwards as far as the umbilicus. The other features noticed were an occasional slight puffiness under the eyelids, some pallor of the face, and towards the end the coat became poor.

A second injection of 2 c.c. of a four days' culture of the Upcott organism was given, 112 days after the first; after which there was an increased tendency to go downhill. It was noticed in the last two months that the animal was not so alert and remained in a sitting posture in one corner of the cage. The appetite throughout was good.

A post-mortem examination was made immediately after the animal was killed, on July 21, 1919. The *peritoneum* was normal. The *liver* projecting below the costal margin was brownish buff in colour, and in parts had a speckled appearance. The *spleen*, $2\frac{1}{2}$ inches long by 1 inch broad, was swollen towards its lower end. The surface showed a slight pearliness with some pin-point thickenings. One adhesion was present on the concave surface. A spleniculus was present in the splenic omentum and a small gland in the gastrosplenic omentum. On section the lower surface was firm, exuded blood, and showed Malpighian bodies. No trabeculae could be seen. The mesenteric glands were not enlarged. The *liver* was generally enlarged and showed three pearly granulomatous scars on the anterior surface. On the under surface of one lobe was a small area with a haemorrhagic border suggesting a red infarct. On section the organ was fatty and slightly bile-stained. No enlarged glands were present in the retroperitoneal tissues. The *kidneys*, *suprarenals*, *stomach*, *intestines*, *heart*, and *lungs* were normal.

Blood counts were made on three occasions. The haemoglobin varied between 76 and 69 per cent., the red blood cells between six and seven million, and the white cells varied between five and nine thousand. The tendency in the counts appeared to be towards a polycythaemia. The fragility of the corpuscles tested on one occasion came out at 0.47 per cent. NaCl.

Cultures. Fifteen separate cultures were made aseptically into dextrose broth, from the spleen, splenic blood, spleniculus, splenic gland, and liver. Four of these were septic after three days or less, and were discarded. Four days afterwards, in seven of the remaining tubes there were found long thin bacilli,

non-motile. In another tube, from which subsequently a typical streptothrix was grown, long chains of streptococci or streptobacilli were found on the third day. The tubes were followed for several months and either the deposit or the portion of the organ reinoculated in serum broth from time to time. In the culture from the gland near the spleen, typical snowball-like growths were observed two months afterwards in the fourth subculture. From the spleen similar growths were observed three months afterwards in the fifth subculture. During the intervening period, long bacilli were detected in these tubes, and their presence prevented their being thrown away as negative. Both cultures were investigated as to their reactions and found to be identical. In all broth media both grew slowly, showing first small flocculi, sinking to the bottom, later forming small snowball-like masses, some of which tended to creep to the surface of the medium. No gas-formation occurred in glucose, lactose, mannite broth, and no alteration of reaction. No change in colour occurred in neutral red lactose broth. Growth on agar occurred in 24 to 48 hours as small circumscribed whitish or buff-coloured colonies, which ultimately created a depression on the surface, and from which they could only be dislodged by digging up the medium. Slight growth occurred on inspissated serum; potato showed no growth and milk was not clotted. Spore formation was absent.

Histology. Spleen: many trabeculae and slight general fibrosis present. The Malpighian bodies showed some central atrophy. No haemorrhagic scars seen. Some veins showed pavementing by leucocytes; others showed thrombi attached to the wall; leucocytes in abundance; general subacute inflammation of walls of veins. Some threads stained by cresylecht violet.

Liver: the atrophic area showed irregular spaces in which were blood cells staining badly, liver cells undergoing atrophy, and some in intermediate stages. Patches of marked fatty infiltration were seen here and there in other parts. Patchy subacute inflammatory changes along the branches of the portal vein extending into the connective tissue of Glisson's capsule. The bile-ducts and artery normal. One branch of the portal vein showed the attachment of a thrombus nearly filling the vein.

Summary. The injection of the organism produced a slow diminution in strength, and emaciation, with enlargement of the spleen and liver. Anatomically there was chronic splenitis with thrombo-angitis and evidence of the same process in the liver with infarction. An identical organism was grown in pure culture from the spleen.

Monkey No. 201. A full-grown *Macacus rhesus*, about one year old. Neither spleen nor liver could be felt in the abdomen. One c.c. of an emulsion in saline of a seven-day agar culture of Upcott's organism was injected intraperitoneally. No symptoms were present either during or soon after injection. Eighteen days afterwards the spleen was felt with two projections on the surface. The liver was enlarged and the edge rounded. No symptoms of ill health were noticed at this time. From that time on until 73 days afterwards, when the animal was killed, it went slowly downhill. The liver and spleen increased in size and the projections on both organs were marked. Emaciation increased, and in the last fortnight feeding was poor.

Post mortem. There was oedema over the pubes and of both ankles, and slight general oedema. Both *liver* and *spleen* showed numerous scattered caseating granulomata, in which tubercle bacilli could easily be found. Small tubercles were present in the omentum, upper lobe of the left lung, and in the lower lobe of the right. The mesenteric glands were tuberculous.

Cultures. Cultures were taken from peritoneal fluid, liver, spleen, and lung. One of those from the lung was contaminated on the second day, and in three from the liver and one from the spleen a short bacillus was found. The cultures were watched for three weeks, but no streptothrix was obtained. No means were taken to isolate the tubercle bacilli.

Summary. Eighteen days after the injection a steady failure in health for 73 days. Death was due to disseminated tuberculous granulomata.

Monkey No. 202. A moderate-sized female *Macacus rhesus* about one year old. On January 15, 1919, 1 c.c. of an emulsion in saline of a 48-hour Upcott agar culture was injected into the right internal saphenous vein. Beyond slight hyperpnoea during the injection, nothing was noticed, and the animal remained well until the ninth day, when the liver was to be felt and the spleen was enlarged to just below the costal margin. From this time on the animal became more seedy, showed diarrhoea, and the coat became poor. The spleen enlarged and showed hard projections, and a large bunch of mesenteric glands was felt near the umbilicus. The animal was killed on the eighteenth day after the injection.

Post mortem. There was considerable emaciation. The liver and spleen were large and studded with caseating tubercles, varying in size from 1 to 10 mm. across. The right pleura was adherent; both lungs showed tubercles on the surface and a mass of caseating tubercles in the right lower apex. There was considerable enlargement of the anterior mediastinal glands. The intestines showed a small chronic ulcer 6 to 7 mm. across in the ascending colon, in relation to which was a large bunch of caseous mesenteric glands.

Cultures. Seventeen culture tubes were inoculated from various organs. No steps were taken to isolate tubercle bacilli, but long threads which failed to grow were present in three tubes from liver, anterior mediastinal gland, and lung.

Histology. The liver, spleen, and mesenteric glands all showed early disseminated caseous tuberculous lesions, and the presence of tubercle bacilli.

Summary. Nine days after the injection there was a rapid decline in health, with diarrhoea and emaciation for eighteen days, when the animal was killed. Generalized tuberculosis was found, with a tuberculous ulcer of the colon. The organism was not isolated.

Monkey No. 203. A young male *Macacus rhesus* about ten months old. On January 18, 1919, 1 c.c. of an emulsion of 48-hour Upcott broth culture emulsified in saline was injected into the internal saphenous vein. No immediate ill effects followed. On the thirteenth day there was an appearance of seediness; the spleen was enlarged and soft; the liver was enlarged, with a projection on the anterior surface. A solid tumour was felt in the region of the stomach. The monkey was losing weight and had some cough. The illness became more and more acute; spleen and liver enlarged, emaciation increased, and there was diarrhoea and some oedema of the face. It was killed forty-seven days after the injection.

Post mortem. There was marked emaciation; caseous glands in both axillae; some peritoneal adhesions; caseous masses both in liver and spleen; tubercles on the under surface of the diaphragm; mediastinal and bronchial glands were enlarged and caseous. There was a tuberculous mass in the upper lobe of the right lung; tubercles on both pleural surfaces. Mesenteric glands were slightly enlarged. Kidneys, suprarenals, and intestines were normal.

Cultures. Sixteen culture tubes of broth were inoculated from various organs. A cocco-bacillus grew from peritoneal fluid, liver, and spleen; but failed to grow on subculture. The rest showed no streptothrix. No attempt was made to isolate tubercle bacillus.

Histology. Early tuberculous caseation of glands and of liver. Abundant tubercle bacilli in the pus.

Summary. Thirteen days following the injection a rapid decline in health for forty-seven days until death from acute disseminated tuberculosis. The organism was not isolated.

Monkey No. 204. A male adult African monkey, *Cercopithecus callitrichus*, in good condition. The spleen could be felt, but no tenderness could be elicited. On July 22, 1920, 2 c.c. of a 48-hour broth culture of Upcott's organism were injected intraperitoneally with no immediate effect. The animal remained in good condition with no tenderness of the abdomen and no alteration of the spleen until October 25, 1920 (97 days), when the lower pole of the spleen was tender. The liver could be felt. Thereafter tenderness was elicited until 17.2.22, when the animal was killed. The amount of tenderness varied considerably, and was present from time to time in parts other than the spleen or liver. The spleen did not increase in size, but appeared to become hard, and could be felt throughout the observation. 23.12.20, 2 c.c. of a 48-hour broth culture of Upcott's organism were injected intraperitoneally. It had been noticed that, for some weeks previous to this date, the animal had been dull. It sat crouched in a corner, whereas the control monkeys were lively, moving about the cage, and alert. Yawning was also noticed. Some irritability was present in January 1921. From being on the placid side, it was more easily roused to temper. 28.2.21, $4\frac{1}{2}$ c.c. of a 5-day broth culture of Upcott's organism were injected intraperitoneally, and after this for a day it refused food. The crouching position never altered, but the legs, from being flexed in the sitting posture for the last six months, showed a tendency to be stretched out. For six months before it was killed, the coat was rough and emaciation was marked. On two occasions mild shivering attacks with a tendency to unconsciousness were noticed. Some breathlessness was noticed a month before death, and from time to time oedema of the eyelids was present; pyorrhoea and pallor of the face was constant in the later stages. The animal was killed 575 days after the first inoculation. The weight of the monkey in the first months was about 2,500 gm. It gradually increased to a maximum of 2,840 gm. nine months after the initial injection of streptothrix. From then onward there was a slow diminution in weight, until one year afterwards it was slightly above that at the beginning, 2,510 gm. From that time until the date it was killed the weight gradually diminished to 2,120 gm.

Blood counts were taken before the experiment and at intervals throughout; eleven in all. The red cells varied from 4,000,000 to 8,700,000; the haemoglobin varied from 66 per cent. to 98 per cent.; white blood corpuscles varied from 5,000 to 19,000. There was a slight increase of red cells, haemoglobin, and white cells as the experiment progressed, but as it was also evident in the controls it cannot be taken into account. The fragility, tested on five occasions, varied very little; full haemolysis occurred at 0.37 to 0.32 per cent. of NaCl. The differential count varied, but no inference could be made from it.

Post mortem. The body was very emaciated. No abnormal glands were found in the groin. The *liver* was atrophied, pale in colour, with one depressed scar on the convexity of the right lobe. On section there was great uniform pallor. One cyst was present. The *spleen*, size 1 in. by 2 in., was normal in external appearance and on section. *Kidneys*: nothing abnormal was noticed. *Pleura* and *pericardium* were normal. The *heart* was normal. *Lungs*: the left lung was very pale but normal in external appearance; the right lung showed numerous petechial haemorrhages on the posterior aspect of the lower lobe. *Spinal cord*: there was nothing obviously inflammatory. *Pelvic organs*: nil. The *intestines* were normal throughout, including the stomach. The *brain* was normal externally, except for a recent haemorrhage over the pons.

Cultures. Twenty-four portions of the body, from spleen, liver, pancreas, and lung, were put into broth with aseptic precautions. Altogether six tubes were contaminated. In three days' time ten tubes showed evidence of a streptococcus; in thirteen days streptothrix threads were present in seven tubes; in thirty-five days streptothrix was found in seven tubes. Streptococci in chains were present in eleven tubes, associated with streptothrix threads in four. None

of these organisms, either streptococcus or streptothrix, grew in subculture. It is possible that the streptococcal threads may have been a stage in the growth of the streptothrix; but subcultures having failed, a decision could not be made.

Histology. The kidney showed hyperaemia and early cloudy swelling. The lung was in a condition of acute pneumonia of the type of acute influenza with oedema and scanty fibrin; and some areas of acute necrosis were present. Thrombi were present in the veins. *Liver:* very early atrophic changes; cellular increase in Glisson's capsule.

Summary. The animal showed a steady decline in health throughout the experiment, during which three injections of the living culture were given; it was killed 575 days after the first injection. A scar of the liver, haemorrhages into one lung, and a meningeal haemorrhage over the pons were all that was found *post mortem*. The organism was not isolated in culture.

Monkey No. 205. A male *Cercopithecus callitrichus*, full grown, showing no symptoms and no tenderness on examination of the abdomen. The spleen could occasionally be felt in front of the kidney, but was not tender when pressed between the fingers. On July 22, 1920, 2 c.c. of a 48-hour broth culture of Upcott's organism were injected intraperitoneally without ill effect. The animal showed no effects of the injection until September 6, i.e. 46 days after the injection, when the spleen was slightly tender. This tenderness of the spleen remained throughout and was often accompanied by tenderness elsewhere in the abdomen. The spleen never enlarged to any marked degree, and from time to time could not be felt by reason of muscular rigidity. Little change in the general condition was shown for five months; the weight varied but little. Generally, the animal became duller than normal, and tended to sit in one corner of his cage. On December 23, 1920, 2 c.c. of a 48-hour broth culture of the Upcott organism were again injected intraperitoneally. After the second injection yawning was noticed to be frequent, often several times in a few minutes. The condition tended very slowly to get worse, though the weight showed little change. Some puffiness of the eyelids and slight pallor of the face were noted from time to time. The crouched attitude tended to become more marked, and the animal was more difficult to rouse than formerly. Tenderness in the abdomen increased. The nature of the animal was rather untamed, and it was noticed about December 1921 that its temper became more spiteful, and one attendant had to be especially careful if near its cage. On May 12, 1922, it was noticed that it was shaky in holding its food, and that on being allowed to go free it climbed into its cage with more difficulty than formerly, both legs and arms being weaker. At this time Dr. F. M. R. Walshe kindly saw it with me, and made the following note:

'The animal retains good power, but the lower limbs are clearly weaker than normal, and the finely co-ordinated movements of the digits in climbing are lost; thus it does not grasp the bars when climbing up the face of the cages, and when resting on a cross-bar, rests on the heel and not on the ball of the foot. Beyond this defect, there is no defect of co-ordination. There is some tremor of the legs, resembling a clonus, as it hangs on to the vertical bars of its cage. The animal can move rapidly and freely about its cage, but in general its agility and activity are less than normal. There is some hypertonus of the lower limb, flexors, and adductors, but active movement renders its determination difficult. The knee-jerks are brisk and show a well-marked "shortening reaction" after each member of a rhythmic series of taps, until the leg from full flexion at the knee comes into partial extension. [This reaction is characteristic of spastic conditions in man and of decerebrate animals.] The lower and upper limb muscles are very tender to pressure. No marked wasting. Pinching of the sole produces fanning and dorsiflexion of the small toes but not of the hallux. Cranial nerves normal.'

From this time onward the same symptoms were noticed, sometimes less, sometimes more; yawning became very frequent. At times the clumsiness of the hands was more marked, and in feeding it would allow the apple or banana to rest on the floor instead of holding it. The appetite never failed, although the power and rate of eating became less. On two occasions it was found lying down in the cage, breathing more rapidly and apparently unconscious, but with no twitching or rigidity. From both attacks it recovered within an hour. Clinically they simulated mild attacks of pulmonary embolism. It was killed on 21.3.23, when it appeared from muscular weakness that proper nutrition could not be maintained; a period of 973 days from the beginning of the experiment. There was a gradual diminution in weight from 3,600 grm. to 2,430 grm.

Blood examinations. These were done at intervals, and before the experiment; but it cannot be said that any inference can be drawn from them. The haemoglobin varied between 78 and 106, the higher figures being towards the end of the experiment. On no occasion was any anaemia found. The red cells were always over 6,000,000, again with a tendency to polycythaemia in the later stages; the last figure five weeks before death being 9,100,000. The white cells varied between 6,000 and 18,000. The differential count showed no abnormality as compared with the controls. The fragility of the corpuscles was tested seven times and found to be uniformly the same, at 0.32 to 0.37 per cent. of sodium chloride for full haemolysis.

Blood cultures were made on four separate occasions, but in no instance was a positive result obtained.

Post mortem. Killed March 22, 1923; examination within an hour. The body was extremely emaciated. The lower limbs flexed on the thighs and difficult to straighten; these limbs were extremely thin. The *peritoneum* was generally inflamed, but no free fluid was present. The *great omentum* was engorged with blood. The *spleen* was small, firm, 3 cm. in length; and on the convex surface was a small opaque pin-head buff-coloured spot. The *liver* appeared natural in shape and size, brownish, slightly transparent in appearance, and swollen on cross-section. No local lesions were discovered and no amyloid change. The *lungs* had several small haemorrhagic areas in the middle lobe towards the base. One of these on section had the appearance of an infarct. On the posterior aspect of both lungs there were numerous small opaque flattened thickenings in the pleura, about 1 mm. in diameter, that suggest healing granulomata. The *kidneys* showed cloudy swelling. The *intestines* were inflamed and catarrhal. The *stomach* showed no ulceration. Exteriorly and on section the brain and spinal cord were normal.

Histology. The *spleen* showed many more trabeculae per low-power field than normal. Only a few Malpighian bodies, and they atrophic, could be identified. Endophlebitis was present in many branches of the splenic vein, and here and there chronic inflammatory changes. The *liver*: slight inflammatory changes along branches of the portal vein; but some sections of the vein showed none. The liver cells were generally fatty. The *lung*: fibrous change was present in scar-like areas and neighbouring changes in the bronchioles. Recent scars were present just under the pleura. The *kidney*: normal except for the presence of fibrous scars. The *spinal cord*: no changes detected.

Summary. A steady decline in health during the experiment, in which three injections were given; the animal was killed 973 days after the initial injection. *Post mortem*, fibrosis of the spleen, portal inflammation, infarct, and scars of the lung were found. The organism was not recovered either during life or from the organs after death.

Monkey No. 206. A small male *Cercopithecus callitrichus*. Nothing could be felt in the abdomen before injections, and no tenderness was present. On July 22, 1920, 2 c.c. of a 48-hour broth culture of the Upcott organism were

injected intraperitoneally. Forty-six days afterwards the spleen and liver were felt and were thought to be harder than normal; they were not tender. Tenderness was definite in the spleen and liver 112 days after the injection, and continued throughout until the animal was killed, 252 days after the injection. The second injection was given on February 28, 1921, after which the tenderness became more marked, and the weight rapidly diminished. One week previous to death some tremor was noticed; later it became unconscious and was killed.

Blood counts. Six blood counts altogether were done, and after the first, in which there were just under 4,000,000 red cells, there was no sign of anaemia either as regards cells or haemoglobin. The animal was in poor condition before the experiment, but improved markedly when put on proper diet. No increase in fragility of the red cells was found (one observation).

Post mortem. There was great emaciation. No glands were found. The spleen was extremely small and shrunken. Ulcers with dark altered blood attached were present in the stomach, small and large intestine; and the intestinal contents were very dark. The liver was not enlarged, but on the extreme edge of two of the lobes were three small pale infarcts, all of which were becoming contracted. A few small haemorrhages were seen in the mesentery and small intestine, and the glands of the mesentery were enlarged. The ulcers in the stomach and intestine had a sharp outline, and penetrated to the muscular coat. In the small intestine were some haemorrhagic patches which had not undergone ulceration. There was marked swelling of the solitary follicles. The section of the liver showed small necrotic bile-stained areas, the size of a largish pin's head. The right lung showed several haemorrhagic areas that suggested infarcts, and one was seen in the left lung.

Cultures were made into twenty broth tubes from heart blood, liver, spleen, and lung. Other tubes were reinoculated from the originals after eliminating those contaminated at the end of eight and twelve weeks respectively; but no growth of streptothrix was obtained.

Histology. *Spleen:* increase of the size and number of trabeculae. The pigment was increased in amount, some located in the pulp along the edges of the trabeculae. The veins were paved with white cells and some phlebitis was present. The Malpighian bodies were atrophied. The arteries were very tortuous and the intima was thickened. Threads of a doubtful streptothrix could be seen in the haematoxylin-stained slides. *Liver:* an area of acute local atrophy and fatty degeneration appeared in one section. There was also slight haemorrhage at this spot. Glisson's capsule showed chronic slight infiltration by inflammatory cells located to the portal vein and its branches. In one of these there was a recent fibrinous embolus. The bile-ducts were normal. Another section showed general slight fatty degeneration of the centre part of the lobule. The same appearances were present in Glisson's capsule as before. In one of the bile-ducts a few bacilli and short threads were found stained by haematoxylin. Interruptions in the threads were present. *Lung:* there was a patchy thickening of the interstitial tissue, and in one section there was a lineal scar in the neighbourhood of a bronchus with atrophied alveoli and pigmentation suggesting a healed infarct. A few small areas of collapse of alveoli and thickening of interstitial tissue in other parts. Bronchi were normal. The intima of the large arteries showed catarrh. This was very marked in the smaller arteries, which showed endarteritis and obliteration of their lumen. Near the obliterated arterials blood cells might be seen in the alveoli.

Summary. Tenderness of the abdomen appeared 112 days after the injection, which was followed by a gradual failure of weight and strength until death 252 days after. There were sclerosis of the spleen, infarcts of liver and lung, and ulceration of the stomach and small intestine. The organism was not isolated.

Monkey No. 207. A small male *Cercopithecus callitrichus*. The abdomen was not tender, and the spleen could easily be felt. On July 22, 1922, 2 c.c. of

a 48-hour broth culture of Upcott's organism were injected intraperitoneally. Four days afterwards there was slight tenderness when the spleen was examined. Fifteen days afterwards the spleen felt hard and tender. Thereafter tenderness was always present in the abdomen on examining either the liver or the spleen. Occasionally tenderness was found elsewhere. On one occasion, 68 days after the injection, the animal had a fit while it was being held for the examination of blood, which lasted for about two minutes and had no ill effects. 154 days after the injection the animal was found to be seedy and died unconscious.

Blood counts. These were done on five separate occasions, and showed slight increase in red cells from 5,000,000 to 7,000,000; no alteration in haemoglobin and the fragility normal.

Post mortem. The *peritoneum* was clear. The *spleen* was small, $1\frac{1}{2}$ inches in length, and was flabby; it showed some perisplenitis, but on section the pulp was firm. Only a few Malpighian bodies were detected. The *liver* was reddish, showed no gross changes, and the cross-section was pale. There were no enlarged glands, and the other organs were normal.

Cultures were made into twelve broth tubes from the spleen, liver, and heart blood. They were watched in the original tubes and in subculture for a period of six months, but nothing grew except a few doubtful bacilli in two tubes. None became septic.

Histology. *Spleen:* there was marked increase of trabeculae; the Malpighian bodies were atrophied; certain areas showed inflammatory changes of a chronic type, and in the veins there were patches of endophlebitis. In the neighbourhood of one of the inflammatory patches there were dilated sinuses filled with blood. A few threads could be seen stained by haematoxylin. *Liver* showed a general fatty degeneration not located to one part of the lobule, and patchy inflammation affecting the portal veins and Glisson's capsule in the neighbourhood.

Summary. Gradual impairment in health from fifteen days after the injection. Tenderness of the liver and spleen. Death after 154 days. Splenic fibrosis and portal inflammation. Cultures were negative.

Monkey No. 208. A small male *Cercopithecus callitrichus*. The spleen could be felt as a short firm organ. This animal was kept as a control under the same condition as the others. No tenderness in the abdomen was ever detected. The spleen was constantly felt, and the animal was lively as compared with the other animals, whose movements were quieter. A marked and regular increase in weight occurred from 1,180 to 1,300 gm. There was a diminution in weight for four months preceding the death of this animal, seven months after it came under observation.

Blood counts. Blood counts, of which eleven were done, showed variation from 5,000,000 to 9,000,000 red cells, from 72 per cent. to 94 per cent. of haemoglobin, and normal fragility.

Post mortem. There was hyperaemia of several organs. No disease was detected in the *spleen*, *liver*, or *intestines*; but both *lungs* showed patches of early broncho-pneumonia. Owing to my absence from Oxford on the date of death, cultures were not made.

Histology. *Spleen* showed general hyperaemia, but no other abnormal change. *Liver* showed hyperaemia, cloudy swelling, and slight fatty degeneration. No evidence of inflammation along the portal spaces. *Kidney* showed cloudy swelling. *Lung:* acute inflammatory oedema with haemorrhage in various parts of a section. The vessels showed no infarction or endarteritis. Some slight catarrh of bronchial and alveolar membrane.

Monkey No. 209. A small male *Cercopithecus callitrichus*, used as a control. No tenderness in the abdomen was ever felt, though the spleen could be detected. The animal was lively and remained normal in every respect from 19.7.20 to

25.10.20, when a note was made that the animal was thin. On 30.10.20 it had been normal at 11.30 a.m., but was found dead about half an hour afterwards.

Blood counts had been done at intervals. The red cells varied between 5,000,000 and 6,370,000; haemoglobin varied between 73 per cent. and 80 per cent., the white blood cells between 8,000 and 22,000.

Post mortem showed two acute ulcers of the *stomach* due to post-mortem digestion, from which the contents could be expressed. No sign of disease was present in any of the organs.

Histology. Neither *liver* nor *spleen* showed any abnormal appearance.

Monkey No. 210. A large adult female bonnet monkey, *Macacus sinicus*, was received on 9.6.21, when a blood count was done. 16.6.21, 6 c.c. of a two-day broth culture of Upcott's organism were injected intraperitoneally. Nineteen days after the abdomen was very tender, deep palpation was impossible, and neither spleen nor liver could be felt. The tenderness remained throughout the experiment, and pallor became marked in the face and mucous membranes six months after the injection. Eleven months after the injection shakiness was apparent in the movements both of arms and legs. It was difficult for the animal to sit upright except by supporting itself by one of the upper limbs. A note of this condition was made by Dr. F. M. R. Walshe, who kindly examined the monkey with me, and is as follows:

'The animal sits propped up against the corner of its cage in a general attitude of flexion. When carefully placed in the open, it maintains this attitude for a few moments, and then falls helplessly on its side in the same attitude, which is more or less fixed by the rigidity of the neck, trunk, and limb muscles. No defect of cranial nerves noted. There is marked general muscular weakness, so that the animal cannot squat upright without support. Such movements of the upper limbs as are seen are feeble and slow, but there is no disorder of co-ordination apart from slight fumbling of the hand and fingers in attempting to grasp a small piece of apple. It can grasp a larger piece and bring it accurately to its mouth. Very occasionally slight tremulousness of the left arm is seen, but there is no error of projection, nor any ataxy. Feeble and limited movements of the legs are seen. The muscular rigidity has produced a "fixation attitude" of general flexion, somewhat resembling that seen in severe cases of paralysis agitans, but differing from this in the extreme weakness present in this animal. The lower limbs are fully flexed, but can be fully extended against the active tonic resistance present. The upper limbs are less rigid (especially the left). The rigidity does not resemble the spasticity of spastic paralysis in man, but rather the diffuse sticky rigidity of paralysis agitans. Possibly there are also secondary changes in the muscle leading to contracture, though there is no actual permanent shortening. It is difficult to estimate the relative value of nervous and muscular factors. No arm-jerks were obtained, but once a doubtful knee-jerk was obtained on the right side. Pinching of the right sole produced a feeble dorsiflexion of foot and small toes, with complete inversion of the foot. No response was obtainable from any other part of the limb.'

This weakness became much greater, and the animal was killed on 23.5.22.

Blood counts were done on five occasions. Red cells varied between 4,900,000 and 7,200,000; haemoglobin between 56 per cent. and 68 per cent.; white blood corpuscles between 7,200 and 22,400. On the three occasions on which fragility of the corpuscles was tested, full haemolysis occurred at 0.37 per cent. NaCl.

Post mortem. Very wasted. Abdominal, chest, and limb muscles normal in appearance and show no fibrosis. Glands in both groins enlarged. *Liver*: natural surface smooth, slightly paler than normal. One place on anterior surface shows increased fibrous tissue in capsule and again on left lobe. *Spleen* shows scarring on convex surface. $1\frac{1}{2}$ in. by $\frac{3}{4}$ in. on section, fleshy. The *peritoneum* was clear. Mesenteric glands (few) normal. The *lungs* were slightly pigmented. An old

healed lesion on the outer surface of the lower lobe of the left lung; otherwise nothing abnormal was seen. The *pericardium* contained no fluid. There was evidence of old pericarditis on the right ventricle and elsewhere less marked. *Kidneys and suprarenals*: normal. *Brain*: on left side of cortex was a depressed scar, yellowish in colour and hard, involving the inferior portion of the ascending parietal lobe, slightly the ascending frontal, angular gyrus, first and second temporal convolutions. Remainder of brain normal. Brain fixed in 10 per cent. saline formaldehyde before section. *Spinal cord* normal externally; no evidence of meningitis, cerebral or spinal. *Stomach and intestines* show no disease. Bones and joints nothing obvious.

Cultures. Seventeen broth-culture tubes were inoculated—ten from the spleen, five from the liver, one from the mesenteric gland, and one from an inguinal gland. On the next day the liver cultures were septic; the rest showed no growth. On 26.6.22, 33 days after inoculation, the growth of a streptothrix was detected in the tube inoculated from the inguinal gland. A possible contamination was present in one of the spleen tubes, but all the others except the liver remained without growth. On 8.7.22, 45 days after inoculation, one of the tubes inoculated with heart blood showed a streptothrix, which, like the first, appeared as small depressed and adherent colonies on agar.

Histology. The *spleen* showed thickening and increase of trabeculae. In the *kidney* was one small healing scar near which were dilated tubules; otherwise it was normal. The *heart muscle* was normal. The *liver* showed periarterial round-cell infiltration and thickening of all coats of arteries with narrowing. In the *brain* section taken through the depressed scar there was general shrinkage and atrophy of cortical layers. Large spaces from which fluid had disappeared in fixation and cutting were also present. The early process was one of fatty degeneration, softening, and atrophy of neurone cells. Some of the arteries were reduced to fibrous cords and the space of Retzius filled with neuroglial cells. The lesion was cerebral softening, with evidence of slight chronic inflammation. Careful staining by special methods failed to reveal streptothricial threads, but in parts the endothelial cells are filled with small bodies, some of which have the form of bacteria, others of round yeast-like bodies. Many of the smaller vessels were blocked with fibrin and inflammation cells; some were more scar-like.

Summary. Nineteen days after the inoculation the abdomen was tender. Thereafter a wasting disease with evidence of nervous complications until the animal was killed, 341 days after the injection. Splenic fibrosis, inflammation of the portal spaces, granuloma of brain. Culture positive.

Monkey, No. 211. A nearly adult female bonnet monkey, *Macacus sinicus*, was received 9.6.21. Weight 2,260 gm. After an initial blood count, it was injected, on 16.6.21, with 5 c.c. of a two-day broth culture of Upcott's organism intraperitoneally. Tenderness of the abdomen became evident 42 days after the injection, though the weight had gone up to 2,420 gm. The tenderness remained throughout. On 12.5.22 it was noticed that the animal was always on its haunches; walking and climbing appeared difficult because of a tendency to flex the thighs on the trunk. Dr. F. M. R. Walshe kindly made the following note on the condition:

'The animal squats in its cage with fully-flexed lower limbs, and moves across its cage "on all fours", partly moving actively and partly dragging its paretic legs after it. It can climb slowly, doing most of the work with its arms, but using the lower limbs to some extent; the extensors of the lower limbs seem weaker than the flexors. Co-ordination of the hands and digits is good, though, from weakness, isolated movements of thumb and index are, perhaps, not so facile as normal. There are no involuntary movements and no ataxy. There is no fixation attitude. It is difficult to estimate the muscle-tone of the limbs, because the animal appears to resist passive movements

actively, but it seems probable that the lower limb flexors are hypertonic (also the adductors of the thighs). The knee-jerks are brisk, R. and L. Pinching the skin of the soles evokes dorsiflexion of the ankle and fanning and dorsiflexion of all the digits; a response clearly resembling the Babinski type of plantar response seen in man. The muscles are not tender to pressure. Cranial nerves normal.

Considerable pallor of the face and mucous membrane developed as the experiment progressed. The appetite was consistently good. The weight, originally 2,260 grm., fell to 1,750 grm.

Blood counts, of which six were made, showed a variation of red cells between 7,000,000 and 9,500,000; haemoglobin between 80 per cent. and 106 per cent.; white blood cells between 8,000 and 17,803.

Blood cultures were done on four occasions; three of these were negative and one positive.

Post mortem. On 20.2.23 the animal was found lying down in its cage, and died soon afterwards. The post-mortem was done eight hours afterwards. Rigor mortis was present. The *peritoneum* was normal. The *spleen* was $1\frac{1}{2}$ inches in length, firm, and had a few thickenings on the concave aspect and the capsule. On section the Malpighian bodies were present, with pulp firm and trabeculae not markedly in evidence. One vein had a thrombus in it; the other veins clear. The *liver* was reddish pink and showed no marked scarring but there was thickening of the capsule on the upper surface of the left lobe. On the anterior surface of one other lobe there was a pale area, but no shrinkage. On section the liver showed no gross changes. The *heart* was dilated, muscle pale, and no changes were seen in the valves. There was no fluid in the pleural cavities. Both *lungs*, however, showed patches suggestive of collapse or atrophy; the left lung especially showed one large atrophied area in the lower lobe with sharp margins. On section of this, a thrombus was noticed in a central main vessel. At the edge of the same lobe there was a small area of solid lung, pale red in colour, suggestive of an infarct. The *stomach* showed two ulcers, one about 1 cm. across, the other about 3 mm., both with attached dark blood. The contents of the *intestine* were not haemorrhagic; the mucous membrane was slightly catarrhal and smelt salty, but was otherwise normal. The mesenteric glands were not enlarged, and no glands elsewhere were enlarged. The *brain* and *spinal cord* showed no evidence of structural change.

Histology. *Spleen*: the trabeculae were thickened and more numerous than normal. The Malpighian bodies were not atrophied. Engorgement of pulp was marked in places, and here and there large sinuses were packed with blood. Under the capsule were areas with slight chronic inflammatory changes. *Liver*: some sections of Glisson's capsule showed cellular infiltration, others not. No catarrh seen. The cells were very fatty. *Kidney*: a small healing granuloma in the cortex. *Lung*: section across the area which, to the naked eye, shows the appearance of an infarct confirmed this. The pulmonary artery in the centre of the mass showed a large fibrinous embolus completely occluding the lumen. The alveoli contained blood cells and catarrhal cells from the walls, which were thickened by recent chronic inflammatory change.

Summary. Tenderness of the abdomen appeared 42 days after the injection. Thereafter, the animal wasted and showed marked paresis of the legs. Death occurred after 614 days. Chronic inflammation of the spleen, Glisson's capsule, lung infarcts, and ulcers of the stomach were found *post mortem*. Blood culture during life was positive.

Conclusions.

A series of ten monkeys of three different species have all shown symptoms of disease after the injection of a streptothrix isolated from a human spleen

removed surgically from a case of recurrent jaundice (acholuric). In three animals (*Macacus rhesus*) it precipitated a rapidly fatal general tuberculosis. In four (*Cercopithecus callitrichus*) there developed a slowly-advancing debility and emaciation with abdominal tenderness and a fibrotic spleen. In three others (*Macacus sinicus*) the same debility and emaciation were produced. One of these had an enlarged spleen, another showed a granulomatous condition of the brain. An identical organism to that injected has been grown in pure culture from the last three animals. Koch's postulates have, therefore, been complied with.

My grateful thanks are due to Sir Charles Sherrington for allowing me to use the facilities in his department, to him and Professor Georges Dreyer for much helpful counsel, to Dr. F. M. R. Walshe for making an exhaustive examination of the animals that showed nervous symptoms, and to Mr. G. Cox for his care for their health and comfort.

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CRITICAL REVIEW

SEPSIS AS A CAUSE OF LYMPHOCYTOSIS

By H. LETHEBY TIDY

It is frequently stated that sepsis is a rare but occasional cause of an absolute lymphocytosis. This statement is apparently based on a very few articles which are constantly referred to.

In my own experience I have never met with an instance where sepsis could be supposed to have produced such a result.

Attention has recently been directed by several observers to the occurrence of an absolute lymphocytosis in glandular fever, which had previously been overlooked. This disease, with its concomitant blood changes, accounts for many of the obscure cases of lymphocytosis recorded in the literature as 'acute leukaemia with recovery', and under other titles.

In the light of these observations I have recently read articles published on the subject of sepsis and lymphocytosis, and propose briefly to review the recorded cases.

I have not attempted to investigate the older literature, and the first article considered is Türk's, published in 1907.

The following are notes of the cases commonly quoted in support of the view that sepsis may produce lymphocytosis.

(The cases will be numbered consecutively for purposes of reference.)

A. TÜRK.

Title of article: 'Septische Erkrankungen bei Verkümmerng des Granulocytensystems'. This may be translated 'Septic Conditions accompanied by Atrophy of the Granular Cell System'.

It will be noted that the title does not refer to an absolute lymphocytosis.

Two cases are quoted:

Case I. Duration of symptoms brief. Admitted to hospital with haemorrhages, purpuric rash, enlarged glands and spleen. Died two days after admission.

Blood: Total leucocytes 900 per c.mm.

Lymphocytes and mononuclear cells 100 per cent.

Evidence of sepsis: Staphylococci in culture from a haemorrhagic bleb.

[Q. J. M., Jan., 1924.]

Case II. Clinical condition typical of glandular fever.

Blood: Total leucocytes 16,700 per c.mm.

Lymphocytes 85 per cent.

Evidence of sepsis: Tonsillitis.

Türk made the diagnosis of acute lymphoid leukaemia, and gave a very bad prognosis. The patient was removed from his care and placed under another physician. A few weeks later Türk heard, to his surprise, that the patient was in perfect health and the blood was normal. He had no idea what the condition was.

B. LÜDKE.

Title of article: 'Über die experimentelle Erzeugung leukämieähnlicher Blutbilder.' This may be translated 'On the Experimental Production of a Blood Picture resembling Leukaemia'. Lüdke is arguing that leukaemia is not infectious, and states that only twice had he seen infection and leukaemia so closely connected that infection as a primary cause could not be excluded.

Case III. A fatal case of acute streptococcal septicaemia.

Blood: Total leucocytes 180,000 per c.mm.

Polymorphonuclear neutrophils 29 per cent.

Myelocytes 45 per cent.

Case IV. The description is confined to the following statement: 'The clinical picture throughout was that of sepsis.' The patient recovered.

Blood: Total leucocytes 82,000 per c.mm.

Lymphocytes 85 per cent.

Evidence of sepsis: Streptococci in blood culture.

C. MARCHAND.

Title of article: 'Über ungewöhnlich starke Lymphocytose im Anschluss an Infektionen.' This may be translated 'On exceptionally marked Lymphocytosis associated with Infections'. Marchand is not especially referring to sepsis, as will be seen from his cases, nor to absolute lymphocytosis.

Case V. Very short duration. Admitted to hospital with extreme anaemia, haemorrhages, enlarged glands, and spleen. Death on the following day.

Blood: Total leucocytes 2,100 per c.mm.

Lymphocytes almost 100 per cent.

Evidence of sepsis: Streptococci isolated from the lungs at autopsy.

Case VI. Boy, aged 14. Previous health: several attacks of 'pyrexial haemorrhagic nephritis'. State on admission: Glands in neck, axillae and groin enlarged, spleen palpable. General pharyngeal congestion. Tonsils swollen, no secretion. Urine contained blood and casts. No oedema.

Blood: Total leucocytes 14,000 per c.mm.

Lymphocytes 90 per cent.

Evidence of sepsis: Presumably tonsils (not definitely stated).

Blood rapidly returned to normal and patient recovered completely.

Case VII. A case of enteric.

Blood: Total leucocytes 3,500 per c.mm.

Lymphocytes 55 per cent.

Case VIII. Record very brief and imperfect. Pneumonia six months previously. Glands and spleen enlarged for a few days.

Blood: Contained 56 per cent. of lymphocytes, apparently with a normal total count.

Patient recovered. There was no suggestion of sepsis.

Case IX. Chronic pulmonary tuberculosis.

Blood: Total leucocytes 9,000 per c.mm.

Lymphocytes 47 per cent.

D. CABOT.

Title of article: 'Lymphocytosis of Infection.' This article is usually referred to in support of the view that sepsis may produce an absolute lymphocytosis. Four cases are recorded, and the first of these cases is the one most often quoted. The account is here given from Cabot's article.

Case X. About 15 years ago a young physician acquired a hangnail infection at an autopsy. This was followed by a mild lymphangitis extending up the arm, with enlargement of the axillary glands both on the corresponding sides and to a lesser extent in the other axilla. There was continued fever for several weeks, with marked prostration. The case somewhat resembled typhoid fever. The blood showed throughout a well-marked absolute and relative lymphocytosis, such that the physician himself and the other consultants were seriously alarmed as to the possibility of lymphatic leukaemia. The record of blood counts was unfortunately not kept, but, if my memory serves me, the percentage of lymphocytes never rose above 70, and the total count of leucocytes never above 20,000. Recovery was rather slow but complete. This physician has had no such an attack since that time, and has remained in good health.

Case XI. A medical student, aged 20, had had boils for six weeks. He then developed a temperature from 100° to 102° for six days. Ten days later the patient was perfectly well. No other clinical data are given.

Blood: Nov. 15, total leucocytes 3,400 per c.mm.

Lymphocytes 82 per cent.

Nov. 20, total leucocytes 15,000 per c.mm.

Lymphocytes 86 per cent.

Evidence of sepsis: Boils.

Case XII. Clinical data suggest a case of glandular fever with an uninterrupted recovery.

Blood: Total leucocytes 9,000 per c.mm.

Lymphocytes 71 per cent.

Evidence of sepsis: Presumably sore throat.

Case XIII. The clinical data suggest a case of glandular fever. Recovery was uninterrupted.

Blood (highest count): Total leucocytes 30,500 per c.mm.

Lymphocytes 67 per cent.

Evidence of sepsis: None mentioned. Fauces not referred to.

E. DEUSSING.

Title of article: 'Über diphtherieähnliche Angina mit lymphatischer Reaktion.' This may be translated 'On a Diphtheria-like Angina accompanied by a Lymphocytosis'. These are cases from an infectious diseases hospital to which the patients were admitted for diphtheria. In all three cases recorded (XIV-XVI)

there was exudation on the tonsils, but no evidence of sepsis elsewhere. The clinical condition in each instance suggests glandular fever, and recovery was uninterrupted. The cultures were negative for Klebs-Loeffler bacillus.

F. SANDERS.

Title of article: 'The Nature of the Lymphocytosis of Acute Infections.' Sanders records a fatal case of leucocytosis. He decides that it was acute myeloblastic leukaemia: this appears to be undoubtedly correct, and the case need not be further considered.

Discussion.

The sixteen cases here reviewed may be divided into the following groups:

I. Cases not bearing on the subject of sepsis and lymphocytosis.

Case I. Apparently acute leukaemia: the only evidence of sepsis was staphylococci isolated from a bleb.

Türk appears to have been perplexed by the leucopenia, but there is no reason to ascribe this to sepsis.

Case III. Blood change in polynucleosis.

Case V. Apparently acute leukaemia, resembling Case I.

Case VII. Typical enteric fever: relative lymphocytosis only.

Case IX. Pulmonary tuberculosis of the lung: no sepsis suggested.

At least three of these five patients died. In none of the remaining cases was there a fatal ending.

II. Cases suggesting glandular fever.

There can be no reasonable doubt that the following six cases were examples of glandular fever, viz. Cases II, XII, XIII, XIV, XV, and XVI. The only sepsis alleged in any of these was tonsillitis, and there was no evidence even of this in Cases II, XII, and XIII.

Case VI is probably glandular fever, but in any event there is no evidence of sepsis.

III. Four cases only remain for consideration.

Case IV. No clinical data are given, and it is impossible to discuss this further.

Case VIII. No sepsis of any kind is recorded in this case. The clinical data which are given are consistent with glandular fever.

Case X. This is the case which is almost invariably quoted in support of the view that sepsis may cause lymphocytosis, but it will be seen that the record is very incomplete.

Case XI. There is evidence of sepsis here in the presence of boils for six weeks previously. The record of the case, which is very brief, is consistent with glandular fever.

It will be seen that the cases of which clinical data are given can be classified with little doubt either as acute leukaemia or as glandular fever. Group C consists of four cases very imperfectly recorded.

It is striking how little evidence of sepsis is present. Cases IV, X, and XI are the only instances of sepsis apart from the tonsils, and in all these cases the record is extremely scanty.

I have not found any account of an absolute lymphocytosis occurring with septic wounds. Nor have I traced any record of a case ascribed to dental sepsis, although such occurrence is mentioned several times in discussions on pyorrhoea and similar subjects.

Conclusion. There is no evidence that sepsis produces lymphocytosis.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

SIXTEENTH ANNUAL GENERAL MEETING

THE SIXTEENTH ANNUAL GENERAL MEETING was held at Edinburgh on Friday and Saturday, May 18 and 19, 1923, in the Department of Physiology, University New Buildings.

Proceedings began at 10 a.m.

The President, Sir Archibald Garrod, was in the chair.

The minutes of the last Annual Meeting, having been published in this Journal, were taken as read and confirmed.

The President referred to the great loss sustained by the Association, since the last meeting, by the death of Sir Norman Moore, who had been President in 1919.

Election of Officers.

President. Dr. Byrom Bramwell was elected as President for 1923-4. On taking the chair Dr. Bramwell expressed the thanks of the Association to the retiring President for his services during the past year.

Treasurer. Sir William Hale-White was re-elected.

Secretary. Dr. H. Morley Fletcher was re-elected.

Executive Committee. Dr. Nixon, Lord Dawson of Penn, Dr. Machie Whyte, and Professor Nesbitt were elected in place of Dr. Charles, Professor Elliott, Professor Gulland, and Dr. Purser.

Election of Honorary Member. Sir Archibald Garrod was elected as Honorary Member.

Election of New Members. On the recommendation of the Council ten new members were elected:

Douglas Kinchin ADAMS, M.D., 12 Lynedoch Crescent, Glasgow. Assist. to Regius Professor of Medicine, Glasgow University.

John Murray BLIGH, M.D., 74 Rodney Street, Liverpool. Physician, Northern Hospital, Liverpool.

John Dixon COMRIE, M.D., 25 Manor Place, Edinburgh. Assist. Phys. Royal Infirmary, Edinburgh.

George HALL, C.M.G., M.D., 1 Eslington Road, Newcastle. Assist. Phys. Royal Victoria Infirmary, Newcastle.

C. E. K. HERAPATH, M.D., Ormlie, Clifton, Bristol. Assist. Phys. Bristol Royal Infirmary.

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F. Gowland HOPKINS, F.R.S., 71 Grange Road, Cambridge. Professor of Biochemistry, Cambridge University.

Edwin MATTHEW, M.D., 9 Walker Street, Edinburgh. Physician, Royal Infirmary, Edinburgh.

Donald PATERSON, M.B., 14 Devonshire Street, W. 1. Assist. Phys. Great Ormond Street Hospital for Children.

George RIDDOCH, M.D., 6 Park Square West, N.W. 1. First Assistant, Medical Unit, London Hospital.

Alexander Gardner ROBB, M.D., 15 University Square, Belfast. Physician in charge of Belfast Fever Hospitals.

Presentation of Treasurer's Report.

The Treasurer, Sir William Hale-White, presented his annual report. This showed a balance of £224 1s. 3d.

Selection of Place of Meeting for 1924.

The Secretary read a letter from Dr. Charles inviting the Association to meet at Bristol in 1924. Some members were of opinion that the 1924 meeting should be held in London. A vote was taken, and by a very large majority it was decided to accept the invitation to Bristol.

This concluded the administrative business.

SCIENTIFIC BUSINESS

FRIDAY, MAY 18. MORNING SESSION, 10.30 a.m.

1. Dr. A. E. Naish gave a record of *two achondroplastic individuals* who begat two normal female children, the parents of the mother being achondroplastic and of the father being normal. These cases, he considered, could not be explained on purely Mendelian lines. He suggested that environment, pre- and post-natal, was the determining factor as to whether the character were recessive or dominant.

2. Lord Dawson related a case of *high blood-pressure* in a young subject of 21 years, attended with severe paroxysmal headaches lasting 24-28 hours. There was a history of scarlet fever at 6. The blood-pressure was persistently high. Both parents exhibited abnormally high blood-pressures. Professor Hopkins had investigated the urine and was of opinion that this contained a pressor substance. Lord Dawson suggested that the condition was one of hyperadrenalism. The normal specific gravity of the urine and the absence of albumin and casts he considered would exclude a renal origin. He discussed the possibility of the pituitary gland as a factor in the case.

This communication gave rise to an interesting discussion, in which Drs. Parkes Weber, Spriggs, and Edgcombe took part. Professor G. R. Murray regarded the case as one of pituitarism and suggested the examination of the cerebro-spinal fluid. Dr. McNee and Sir Humphry Rolleston were in favour of a renal cause of the high blood-pressure.

3. Dr. A. F. Hurst recorded a case of *Addison's disease* in a man of 41 apparently cured by suprarenal grafting. An adrenal gland from an 8 months' foetus was grafted into the testicle. Great improvement had resulted; the blood-pressure had risen from 75 mm. to 120 mm., and the patient was able to do light work, though the pigmentation remained unaltered.

Dr. Hume and Dr. Theodore Thompson had both tried the same procedure in cases of Addison's disease, but without successful results.

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Professor A. G. Gulland was of opinion that the administration *per os* of suprarenal extract was of definite value in early cases of Addison's disease. He referred to the difficulty which might arise in differentiating cases of pernicious anaemia from those of Addison's disease. He considered that adrenal extract was of use in some early cases of pernicious anaemia.

Dr. Byrom Bramwell related a case in which marked improvement followed the administration of suprarenal extract.

Sir A. Garrod and Dr. W. Hunter joined in the discussion.

4. Dr. J. Eason and Dr. H. Whitridge Davies gave a communication on the relation between *metabolism and blood-pressure in diseases of the thyroid*. A fairly close and constant co-relation between the metabolic rate, pulse-rate, and blood-pressure under basal conditions in thyroid diseases was shown in 118 records. A rise in the metabolic rate was associated with a corresponding increase of the pulse-pressure and pulse-rate. They considered such simultaneous observations had value as controls against error.

Dr. R. Hutchison and Professor Murray were of opinion that observations of the pulse-rate and of the body weight in thyroid disease were sufficient for clinical purposes.

5. Dr. Geoffrey Evans related two cases of *mononucleosis*. In both there was pyrexia and swelling of the lymphatic glands, and in one the liver and spleen were enlarged. In both there was a moderate leucocytosis, but the striking feature was the large number of large mononuclear cells—85 to 90 per cent.

Sir W. Willcox gave some further details of the second case, which he had seen with Dr. Evans.

Dr. Tidy had seen 8 cases of mononucleosis and could see no difference between these and cases of glandular fever. 35,000 leucocytes with 80 per cent. mononuclears was the highest count he had found.

6. Dr. Mackenzie Wallis gave his experience of the tests for *hepatic insufficiency*, more especially in the investigation of the effects produced in the liver by injections of salvarsan, &c. He had employed the laevulose tolerance test and the estimation of the lipase and cholesterol control of the blood. He regarded the lipase test as one of the most valuable. In degeneration of the liver the lipase content of the blood showed a rise. He predicted that cases of subacute degeneration of the liver would become more frequent owing to the increasing administration of arsenical compounds, copper salts, benzene compounds, &c.

2 to 3 p.m.

Demonstrations were given in the Research Laboratory of the Royal College of Physicians by Dr. H. D. Wright and Dr. W. D. Kermack on *colloidal gold and benzoin reactions in the cerebro-spinal fluid*, and by Dr. G. Marshall Findlay on *changes in the bones and bone-marrow as the result of deficient diets*.

A demonstration of clinical cases was given at the Royal Infirmary.

3 p.m.

1. Dr. J. Crichton Bramwell described a method of measuring the velocity of transmission of the pulse-wave in man. The results obtained showed that in healthy subjects velocity varies regularly with age, suggesting that the variation of systolic blood-pressure with age is a compensatory mechanism to make up for the loss of arterial elasticity. Observations on isolated human arteries removed *post mortem* showed a characteristic relationship between pulse-wave, velocity, and pressure. This relationship is lost in calcareous arteries. In subjects whose diastolic pressure is very high or whose arteries are calcareous, even a high pulse-pressure and an increased pulse-rate will enable the arteries to accept only a small ventricular output per minute. This limits the oxygen supply to the tissues and the physical capacity of the patient.

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Dr. Langdon Brown pointed out that the determination of the velocity of the pulse-wave was of importance in prognosis.

2. Professor J. Meakins and Dr. H. Whitridge Davies made a communication on the output per heart-beat and the minute volume of blood-flow in health and in certain cardiac diseases. In normal adults the minute volume of blood-flow varies from $5\frac{1}{2}$ to 8 litres, according to size and sex. This increases when the metabolism is increased, as, for instance, during exercise, and may amount to 20 to 30 litres per minute. A similar state of affairs exists in pathological increases of metabolism, as in exophthalmic goitre. The output per heart-beat may remain constant or be increased in different individuals and even in the same individual under varying conditions of general health. The principal means, however, whereby the blood-flow is increased is by an increase of heart-rate. In mitral stenosis the output per minute and per beat is conspicuously diminished. The former can only be increased by an increase of rate and sometimes at the expense of the latter. In these cases the blood-flow per minute seldom exceeds that of normal persons at rest. In mitral insufficiency the blood-flow per minute is not as a rule affected unless cardiac failure be present. The same applies to aortic disease, but if cardiac failure supervene the minute blood-flow and also the output per beat are greatly diminished: this latter phenomenon signifying incomplete systolic contraction, even though the area of cardiac dullness is increased. This incomplete systole is probably one of the most important factors in cardiac failure. In auricular fibrillation and flutter and in paroxysmal tachycardia the circulation rate is diminished to an extreme degree, whilst the output per beat is diminished with the increase of rate. Therefore increased rate does not produce increased output, but rather the reverse.

3. Dr. E. P. Poulton made a communication on the *differential diagnosis of lesions in congenital heart disease*. The most commonly accepted explanations of the cause of the cyanosis are that it is due either to an admixture of arterial and venous blood or to stasis at the periphery. Patency of the interventricular septum brings about the mixing of arterial and venous blood. If oxygen be given by a gas mask, cyanosis lessens, but does not vanish if the septum is patent. If the septum be closed the cyanosis disappears.

Professor Meakins described another method for differentiating between the two conditions: the arm is placed in very hot water; if a case of pure pulmonary stenosis, the hand will become quite pink, whereas if the septum be patent the cyanosis will persist.

Professor Wardrop Griffith referred to the relationship between the polycythaemia and the cyanosis, and related two cases of congenital heart disease with very extensive lesions, but without cyanosis.

Professor Kauffmann, Sir A. Garrod, and Sir H. Rolleston joined in the discussion.

4. Professor F. R. Fraser (with T. P. Dunhill and A. W. Stott) described the results obtained by the use of *quinidine* in 15 cases of *thyrotoxic auricular fibrillation*.

5. Dr. John Poynton discussed the possibilities of *preventive treatment for heart disease in the young*. He pointed out the futility of drugs, vaccines, and sera in the treatment of organic heart disease. He considered the evidence of an infective cause of rheumatic heart disease was overwhelming. He urged the better education of medical students in diseases of childhood, and propaganda amongst the public and to school teachers. He pointed out the need of an auxiliary hospital for heart cases, attached to the general hospital, and the importance of selection of suitable occupations for the patients.

Drs. Tyson, Melland, Ryle, and Mantle endorsed the views expressed by Dr. Poynton.

Dr. Cameron suggested that the lessening number of cases of acute rheumatism in children of hospital class might be due to the increasing attention and care devoted to the nasopharynx in school children.

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6. Dr. W. Gordon pointed out the value of change of posture as a means of distinguishing between *pericardial friction* and *aortic regurgitation*. The friction sound might disappear when the recumbent position was changed to the erect or vice versa, whereas an aortic regurgitant murmur persisted.

7. Dr. V. F. Cotton gave a communication on *enlarged spleen as a sign of subacute infective endocarditis in chronic valvular disease of the heart*. He pointed out that enlargement of the spleen occurs most frequently in cases with aortic disease, and that this type is the most fatal.

The Annual Dinner was held at 7 for 7.30 p.m. in the Hall of the Royal College of Physicians. The President, Dr. Byrom Bramwell, was in the chair and 120 members and guests were present.

The official guests were: The Right Hon. the Lord Provost, the Dean of the Chapel Royal and of the Order of the Thistle, the President of the Royal College of Physicians of Edinburgh, the President of the Royal College of Surgeons of Edinburgh, Professor A. R. Cushny, Sir Norman Walker, Dr. J. Hamilton Crawford, Dr. Marshall Findlay, Dr. C. G. Lambie.

SATURDAY, MAY 19, 10 a.m.

1. *Insulin*. Communications were made by five members representing the five insulin centres.

Professor Maclean opened the discussion and referred to the difficulty of preparation of insulin, its sterilization, filtration, standardization, and the dosage.

Professor Meakins recorded his experience with regard to insulin treatment of cases of diabetic coma, and of acidosis, and to the avoidance and treatment of hypoglycaemia.

Professor Mellanby discussed the influence of insulin on the metabolism of the various food-stuffs.

Dr. Cowan dealt with the regulation of the dosage of insulin. He agreed with the majority of those investigating the subject, that if insulin were given twice daily, the larger dose should be given in the morning and the smaller in the afternoon.

Dr. George Graham emphasized the importance of carbohydrate restriction in cases treated with insulin. He was of opinion that whenever sugar appeared in the urine the islands of Langerhans were overworked.

Dr. Poulton related a case of diabetes which proved refractory to insulin treatment.

Dr. Spriggs gave details of the result of treatment with insulin of a chronic case of diabetes.

2. Dr. E. S. Reynolds related two cases in which *injury appeared to be the possible cause of brain tumour*. He quoted various authors' statistics in support of the view that brain tumour might result from injury to the head, and sought information from members as to their experience of such relationship.

Dr. Taylor and Sir W. Hale-White were of opinion that there was some connexion between injury and brain tumour.

Dr. Buzzard could not recall more than one instance of head injury during the war followed by brain tumour.

Dr. Byrom Bramwell held the view that injury might cause tuberculous tumours and also gliomatous growths.

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3. Dr. Parkes Weber related a case of chronic *Hodgkin's disease* of the cervical glands in a young man. Subsequently *paraplegia* developed, which was found *post mortem* to be due to lymphogranulomatous growth with the spinal canal between the dura mater and the periosteum. He referred to the literature bearing on the subject.

Professor Kauffmann and Dr. Buzzard had seen similar cases.

Sir W. Hale-White had seen one in which the brachial plexus was involved.

Sir H. Rolleston regarded this rare complication as a further change in the disease, i.e. lymphadenoma becoming sarcomatous. He had seen several cases of this kind.

4. Dr. C. P. Symonds discussed the *pathological anatomy of disseminated sclerosis*. In a case he had investigated the perivascular spaces contained fat granules, and in some there was definite leucocytic infiltration. He concluded that in the acute stage there might occur a true inflammatory reaction which gave ground for the belief that the disease might have an inflammatory origin.

Dr. Byrom Bramwell referred to his own early published observations on the presence of fat granules in disseminated sclerosis.

5. Dr. C. J. Macalister made a communication on *chorea resulting from stock brain influences*. He discussed the relationship between chorea, left-handedness, and stammering. Chorea is liable to occur in children who are right-handed but have stock brain influence of left-handedness.

Dr. Byrom Bramwell also spoke.

2-3 p.m.

Professor Cushny gave a demonstration in the Pharmacological Department.

Professor W. Russell gave an epidiascopic demonstration on arterio-sclerosis.

A collection of clinical cases was shown at the Royal Infirmary.

3 p.m.

1. Dr. J. F. Gaskell gave the results of his work on the *experimental production of pneumonia*. He drew attention to the importance of small bronchioles branching directly off the largest bronchi in the lung of the rabbit. In injections of the lungs in rabbits low virulence cultures are 'side-tracked' and dealt with in the centre of the lobe, causing a central pneumonia. Cultures of higher virulence are more widely distributed and give rise to a lobular pneumonia, whilst cultures of still higher virulence spread through the whole lobe and produce a lobar pneumonia. He regarded lobar pneumonia as due to infection conveyed by the air-passages and not by the blood.

Dr. Byrom Bramwell and Dr. Tidy discussed the communication.

2. Dr. A. G. Gibson described the results of experiments on the *aetiology of chronic splenic infections*. Organisms obtained from a case of acholuric jaundice were found to be pathogenic in monkeys, producing debility, enlarged abdomen, and ultimately death. In one only was there an enlarged spleen. In none was found fragility of the red blood corpuscles.

3. Dr. A. Goodall and Dr. W. A. Alexander (introduced) related a group of cases of *myelocythaemia* with *chloromatous growths*. They suggested that both the leukaemia and sarcoma might have an infective origin.

Dr. Byrom Bramwell referred to cases he had described many years previously which presented features similar to those under discussion.

4. Dr. J. A. Ryle related two cases of *steatorrhoea due to obstruction of the lacteals*. The first, a female of 23, was subject to diarrhoea since infancy with attacks of tetany at intervals. The stools were unformed, bulky, and pale, and contained an excess

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of fat as globules. Laparotomy revealed extreme dilatation of the lacteals due to pressure by caseous tuberculous glands. The second, a male of 36, had tuberculous glands in childhood. The stools were similar to those in the former case. Laparotomy showed tuberculous mesenteric glands and enormously disturbed lacteals. He discussed the possible relationship between these cases and coeliac disease, and pointed out the importance of demonstrating the absence of obstruction to the thoracic duct or lacteals in cases of reputed coeliac disease.

Dr. Poynton referred to the post-mortem examination of a case of coeliac disease in which oedema and ascites were present. No gross change was found in the lacteals. The thoracic duct was not examined. The abdominal lymph glands were usually swollen in coeliac disease, but were not tuberculous. He emphasized the importance of limitation of the fat intake in coeliac disease.

Professor Meakins related an adult case with fatty stools and diarrhoea of long duration. In this the mesenteric glands and the lacteals were full of fatty acids which had a glistening appearance.

Dr. Spriggs and Dr. Hurst also spoke.

Sir A. Garrod urged that the term steatorrhoea should be limited to cases of pancreatic disease and to the congenital type.

5. Dr. G. E. Nesbitt discussed *chronic partial duodenal obstruction* as a cause of dyspepsia. The cause of the obstruction varied, but was most commonly due to the superior mesenteric artery owing to the dropping of the colon.

Dr. Hurst pointed out that the essential point of diagnosis was the X-ray appearance of active duodenal peristalsis passing backwards and forwards into the stomach.

Dr. Nesbitt also related a case of *primary cancer of the liver* in a patient of 21.

6. Dr. John Eason, with Dr. Malcolm Smith and Dr. Buchanan (introduced), related cases of *nephritis occurring in three brothers aged 18, 19, and 20, and one sister aged 10*. Blood Wassermann reaction was negative: the blood-pressure was high in all the cases. Micro-organisms were found in the blood and urine of some of the cases.

Dr. Hurst gave details of a family history of nephritis which he stated was the longest on record, eleven cases in three generations.



THE VARIATIONS IN GASTRIC SECRETION OF THE NORMAL INDIVIDUAL

By JAMES R. BELL AND WILLIAM MACADAM

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Introduction.

THE fractional method of gastric analysis as introduced by Rehfuess (1) in 1914 has reopened the question as to the value of examination of the stomach contents. Notwithstanding considerable criticism of the new technique, especially as to the value of the findings not being commensurate with the labour involved, it is gradually being more widely adopted in the routine investigation of gastrointestinal and other conditions both in America and in this country. Even in its present form and with our meagre knowledge of the probable normal standards and possible variations, the fractional method supplies much more information than the single one-hour test, upon which many of our present-day views are based.

In order that the results obtained in pathological conditions may be assessed at their true value, it is essential that we should know what variations in secretion and motility may occur in the normal individual when subjected to this method of investigation.

Bennett and Ryle (2), with this object in view, investigated one hundred healthy medical students and recorded their findings in an admirable paper. Rehfuess, Bergeim, Hawk, Fowler, Zentmire (3), (4), (5), and others also examined series of normal individuals of both sexes, but so far as we are aware there is no published record of a series of fractional test-meals carried out over a prolonged period in the same individual under constant conditions. The only references we have been able to find with regard to the daily variations in the acid-curves of a normal individual are contradictory. Lyon, Bartle, and Ellison (6), in remarking on the variations in the acid values in different normal persons, say 'if the stomach contents of the same individual are examined daily under the same conditions of time and length of preceding fast, great variations of acid values will frequently be seen'. Bennett and Ryle (2), on the other hand, affirm that 'in several instances exactly identical curves have been obtained when taken on different occasions; in general, it has been found that slight differences may be found towards the end of the curve, corresponding with the amount of duodenal regurgitation at a particular moment'.

We therefore considered it desirable to study the variations in gastric response to the same test-meal repeated under the same conditions on twenty consecutive days (Sundays excepted), in a healthy subject. At the same time the opportunity was taken of comparing these findings with those obtained with several other types of test-meal in general use.

Method of Procedure.

The investigations were carried out on a healthy man, aged 31 years, weight 10 st. 4 lb., height 5 ft. 6 in., of good physique, no previous illnesses, and no history of any gastro-intestinal disturbance whatever.

After a preliminary examination of several individuals, we purposely selected this subject as his stomach showed a good secretory response to the meal, while he displayed an intelligent interest in our experiments and underwent the examination without any apprehension or discomfort. As far as possible he observed the same daily routine with regard to meals and habits throughout the whole period of investigation. He took no food or drink after 10 p.m. and each morning at 9.30 he swallowed a Ryle tube. The fasting contents of the stomach were completely withdrawn and the standard test-meal of oatmeal gruel, as employed by most workers on fractional gastric analysis, was given. Subsequently 10 c.c. specimens were aspirated at intervals of a quarter of an hour for $2\frac{3}{4}$ hours. As is so commonly the case, there was moderate salivation during the test. Measures were therefore taken to avoid swallowing this saliva, the amount collected during the $2\frac{3}{4}$ hours averaging 250–300 c.c. For further details of the method we would refer to the description given by Ryle (7), the first communication on the subject to be published in England.

The term 'free HCl curve' as applied to the series of acidities obtained on titrations with dimethyl-amido-azo-benzene as indicator is doubtless open to serious criticism. As shown by Bolton and Goodhart (8), this curve is not a measure of the actual gastric secretion, but represents only the balance between the two processes—gastric secretion and neutralization mainly by regurgitated duodenal contents. The term may be retained if this restricted connotation be borne in mind.

Our object was the investigation of the range of variations to be met with in a normal subject by the use of a method extensively used in clinical medicine. The estimation of total and inorganic chlorides is certainly a more accurate measure of gastric secretion, but the time and labour required in carrying out thirteen such estimations in connexion with one fractional test-meal, such as that under discussion, renders the method impracticable as a routine clinical test.

Discussion of Results obtained.

Reproductions of the charts illustrate the points of similarity between the curves and such daily variations as were present more clearly than a composite

chart or verbal description. The first impression obtained from a study of the charts is that there is marked dissimilarity between them. Closer examination shows that this is dependent on daily fluctuations in the acid values of the different 'fractions', and that, with the exception of the first and possibly the third curves, the remainder exhibit many points of similarity and are of the same type.

From the practical standpoint, the fact that the lowest curve of the series was that obtained on the first examination raises an important question. In the ordinary course, this is the curve that would have been taken as representing the secretory activity of this individual's stomach. It would have been classed as a 'normal', according to the scheme adopted by one of us (9). As to the factor or factors responsible for this low secretion as compared with the subsequent examinations, we are inclined to the view that it is a psychical inhibition due to the natural apprehension so commonly noted on the first occasion of swallowing the tube. Bennett and Venables (10) have demonstrated this effect of the emotions on gastric secretion. In our opinion nausea did not play much part in the secretory inhibition in this case; nor did the reputed neutralization of the acid by swallowed saliva take place, as this was carefully avoided throughout the whole series of examinations.

This observation points to a possible fallacy in the investigation of pathological conditions, and suggests that if on the first examination a hypochlorhydric or normal curve is obtained, and even more so if the clinical evidence suggests a higher curve of acidity, the test should be repeated before eliminating the possibility of a higher acid secretion.

It may here be mentioned that on two occasions on which the alkalinity of the saliva was estimated it was found to require for neutralization 30 c.c. N/10 HCl per 100 c.c., while the total amount secreted averaged 300 c.c. Such an amount of alkali distributed over the 2½ hours will lower the acid curves slightly. We accordingly carried out two tests whilst the patient swallowed all saliva. No appreciable difference was to be observed in these curves as compared with those of the series already discussed. It is obvious, however, that such a factor might play a part in leading to a low acidity in a subject who was not of the 'hyperchlorhydric' type.

Type of Acid-curve.

It is not to be expected that an individual's curve of gastric acidity during a test-meal will exhibit exactly the same characteristics on every occasion, for many factors, both known and unknown, may cause slight deviations. However, in such a subject as we have examined and under conditions as nearly constant as possible, we should anticipate *a priori* that the acid-curves on the various occasions would show some constant characteristic feature, although possibly differing in detail. Such is seen to be the case, for, almost without exception, it is apparent that the meal provokes an immediate abundant

secretion of acid. The curve of acidity loses very little time in rising to a considerable height, which is more or less maintained until digestion has been completed (as determined by the negative starch-iodine reaction which marks the time of emptying of the stomach). Thereafter it quickly falls to a level approximating to that of the fasting contents, to be followed by a slight rise which is maintained to the end of the test. This common characteristic of the various curves is most striking, notwithstanding the wide variations in the degree of acidity. Thus if we exclude the first and the third, all the curves would be classified either as mild or definite hyperchlorhydria. Another noteworthy point is that the curves of free HCl and total acidity bear the same relation to each other throughout the series.

Experience in fractional gastric analysis soon teaches the observer the folly of laying stress upon slight deviations in the curves, and leads him to rely more and more for his deductions on the type of curve taken as a whole. Ryffel (11) has already emphasized this point, and the present findings afford ample evidence of the necessity of taking this precaution.

Fasting Contents of Stomach.

The amounts obtained varied between 3 c.c. and 38 c.c., with an average of 17.8 c.c. This variation is in accordance with Ryle's (12) experiments on himself, in which over a period of thirty days the amount varied from '1 or 2 c.c. obtained with difficulty to 15 or 30 c.c. obtained with ease'.

The free HCl values varied between 0 and 22, averaging 8.5, and the total acidity values between 8 and 40, averaging 23.4. Ryle's corresponding figures were 0 to 22 and 4 to 38. These variations are to be expected, for duodenal reflux, swallowed saliva, and presence or absence of hunger sensations must necessarily vary from day to day. On only one occasion was bile visible in the fasting contents, and then in very small amount.

Rate of Emptying of Stomach.

This was a remarkably constant feature. The average time of emptying was 1.6 hours, with a range from 1.5 to 2 hours. This finding was confirmed by X-ray examination, for the report of which we are indebted to Dr. Leo A. Rowden, of Leeds. He says, 'This individual's stomach is normal in every respect. It is orthotonic in type, and peristalsis is of normal activity. After a meal of one pint of oatmeal gruel containing 2 oz. of bismuth carbonate the stomach was empty in 1½ hours.'

Application of Statistical Methods.

As may be gathered from our previous remarks, although the results of gastric analysis are conveniently recorded by the graph method, we do not

consider that statistical methods can be reasonably applied to the elucidation of such curves. A false impression of mathematical exactitude is thereby suggested which is wholly misleading when applied to a phenomenon which physiologically varies within such wide limits.

We have, however, submitted our figures to Dr. Matthew Young, of the Medical Research Council statistical department, and are greatly indebted to him for working out the standard deviation, i.e. the degree of scatter or variation in the distribution of the different acid values. This is recorded in Table I along with the coefficient of variation which enables us to compare the several distributions as regards the degree of variation present. One interesting fact emerges from this study, viz. the coefficient of variation for both

TABLE I.

Specimen.	Free HCl.			Total Acidity.		
	Average.	Standard Deviation.	Coefficient of Variation (%).	Average.	Standard Deviation.	Coefficient of Variation (%).
Fasting juice	8.50	8.115	95.5	23.45	9.764	41.6
$\frac{1}{4}$ hr.	3.80	7.586	199.6	23.75	10.449	44.0
$\frac{1}{2}$ hr.	24.80	16.497	66.5	51.45	18.159	35.3
$\frac{3}{4}$ hr.	47.50	18.800	39.6	70.15	17.431	24.8
1 hr.	56.35	14.523	25.8	74.10	13.924	18.8
$1\frac{1}{4}$ hr.	48.26	17.474	36.2	62.63	17.824	28.5
$1\frac{1}{2}$ hr.	41.60	20.375	49.0	55.35	20.558	37.1
$1\frac{3}{4}$ hr.	33.65	19.239	57.2	46.85	19.691	42.0
2 hr.	27.26	15.617	57.3	40.47	16.359	40.4
$2\frac{1}{4}$ hr.	26.40	15.406	58.4	40.10	14.798	36.9
$2\frac{1}{2}$ hr.	29.15	12.130	41.6	42.00	13.472	32.1
$2\frac{3}{4}$ hr.	31.00	14.287	46.1	44.11	14.843	33.7

The average values of free HCl and total acidity calculated in terms of c.c. of $\frac{N}{10}$ NaOH required to neutralize 100 c.c. gastric juice, together with the standard deviations and coefficients of variation of the various specimens.

free HCl and total acidity is lowest in the one-hour specimens. That is to say, if reliance has to be placed upon the examination of a single specimen, then that withdrawn at the end of one hour appears to give the most constant values for the degree of acidity. From the statistician's standpoint, however, it must be noted that the coefficient of variation in this fraction is still very considerable, viz. 25.8 per cent. and 18.8 per cent. for the free HCl and total acidity respectively.

Comparison between various Test-meals.

On completing the series of twenty consecutive examinations with the standard test-meal, we investigated some of the other meals commonly employed, with the following results:

1. *Two slices (60 grm.) of bread without crust, and 500 c.c. water.* The curves conformed in every way with those obtained in the above series, and the stomach emptied at the same rate. If, therefore, the oatmeal gruel meal is

not available, the bread and water meal will give the same information, and data obtained with this meal may be fairly compared with those obtained with the oatmeal gruel. Nevertheless, we would not advise bread and water as the routine meal, for, unless the tube is re-swallowed after the fasting contents of the stomach are withdrawn, efficient mastication of the bread is somewhat difficult and the small holes in the tube are more liable to become blocked.

2. *Two slices (80 grm.) of toast without crust, and 400 c.c. tea with milk and sugar.* The curves approximated to the higher ones obtained in the above series and exhibited exactly the same characters. The rate of emptying of the stomach was unaltered. No difficulty was experienced in withdrawing the specimens, nor in their titration, but owing to the brownish colour the end-point was not so distinct. Moreover, bile and blood in small amounts could be easily overlooked.

3. *60 grm. of arrowroot biscuits and 500 c.c. water.* The curves obtained resembled the lower ones in the above series and manifested the same general characters. There was, however, a greater divergence between the curves of free HCl and total acidity in the earlier stages of digestion. This is probably due to the more finely divided particles being able to 'mop up' more readily the acid secreted. The specimens withdrawn were extremely homogeneous. The rate of emptying of the stomach was unaltered.

4. *Peptone 5 grm., sod. salicyl. 0.1 grm. in 250 c.c. water.* (As recommended by Delort and Verpy (13).) A rapid rise in the free HCl curve results, so that the highest value (70) is reached in 45 min. The descent in the curve is equally rapid, no free HCl being found at the end of $1\frac{1}{2}$ hours. No trace of sodium salicylate was to be found at the end of half an hour, the evidence accepted by Delort of complete evacuation of the stomach.

5. *Two pints of standard oatmeal gruel.* The curve obtained with this 'double' meal made a more gradual ascent than those in the above series, and did not reach its fastigium (which was 60 units for the free HCl) until $1\frac{1}{2}$ hours had elapsed. The descent was also more gradual, and altogether the curve did not resemble at all closely those hitherto obtained. The rate of emptying of the stomach was only slightly, if at all, delayed.

Summary.

1. A study has been made, by means of the fractional method, of the gastric response of a healthy individual to the same test-meal, under the same conditions, on twenty consecutive days.

2. The lowest acid-curve of the series was obtained at the first examination. Subsequently, with one exception, the curves of 'free HCl' and total acidity were of a characteristic type and the degree of acidity varied between a mild and a definite hyperchlorhydria. They serve to show, however, the range of variation which may occur in the same individual in a series of examinations.

3. The rate of emptying of the stomach was remarkably constant throughout the whole investigation, and was confirmed by X-ray examination.

4. The 'standard deviation' and the 'coefficient of variation' of the acidities of the different specimens at corresponding times were determined. The coefficient of variation for both free HCl and total acidity was lowest in the one-hour specimens. That is, the acid values of this fraction varied within the narrowest range.

5. Several of the other test-meals in common use were employed and the results obtained compared with the 'oatmeal gruel' series. The 'tea and toast' meal provoked a slightly greater acid secretion than the average one obtained with oatmeal gruel.

6. One practical point emerges, viz. if a low or normal acid-curve is obtained on the first examination, when the clinical history of the patient suggests a hyperchlorhydria, the test should be repeated before a high degree of acidity can be eliminated.

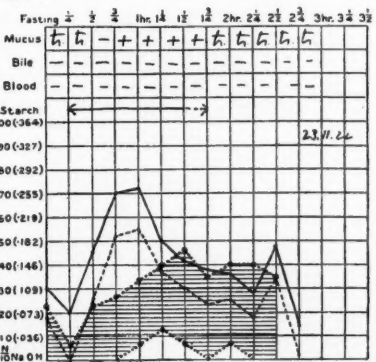
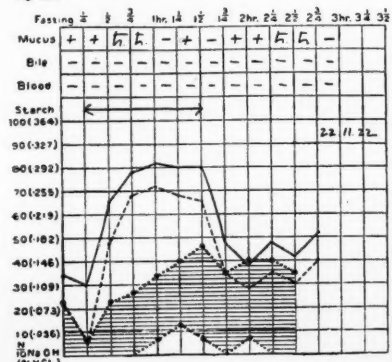
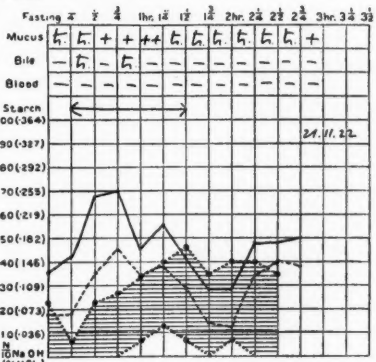
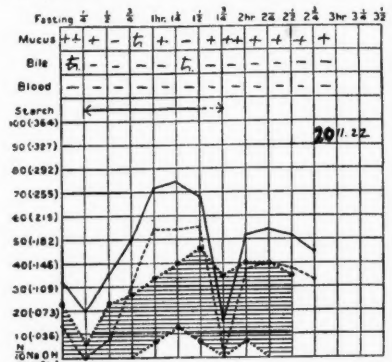
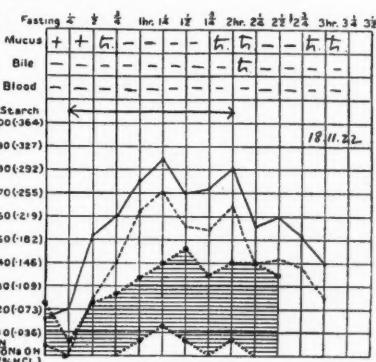
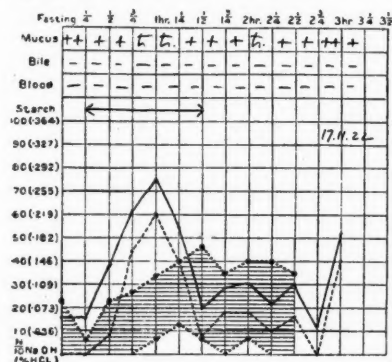
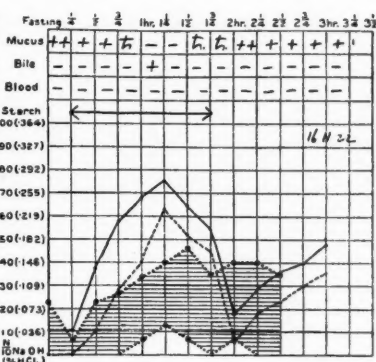
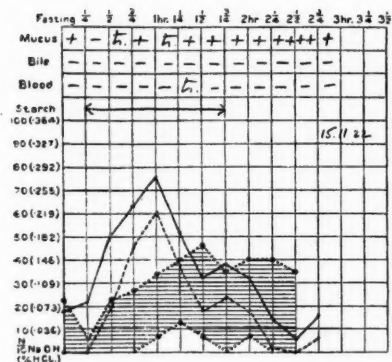
In conclusion, we wish to express our thanks to Professor M. J. Stewart for affording us facilities for carrying out this investigation in the Pathological Department of the University of Leeds.

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VARIATIONS IN GASTRIC SECRETION

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ARTERIAL ELASTICITY IN MAN

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With Plate 17

I. *The Relationship of Pulse-wave Velocity to Arterial Elasticity.*

THE mechanism of the heart is so much more complex than that of the arteries that most workers, in studying the mechanics of the circulation, have devoted their attention to the former rather than the latter: and, in consequence of the paucity of experimental observations on the subject, we have but little accurate knowledge of the extent to which the functional efficiency of the arterial wall is affected by different physiological and pathological conditions. The present research was undertaken with the object of obtaining quantitative measurements of arterial elasticity both in health and in disease, with a view to determining the influence of this particular function on the circulatory mechanism as a whole.

In the living subject, it is not possible to measure arterial elasticity directly; but, since the velocity with which a wave of pressure is transmitted through fluid contained in a tube depends, other things being equal, on the elasticity of the walls of the tube, from measurements of the velocity of transmission of the pulse-wave the elasticity of the arterial walls may be calculated. The original formula put forward by Moens (20) in 1878 to correlate arterial elasticity and pulse-wave velocity is of little value for practical purposes, since it contains three unknown factors which vary in different arteries, and none of which are easily measurable. It has, however, been shown by Bramwell and Hill (3) that the relationship between velocity and elasticity may be expressed very much more simply. It can be shown that:

$$\text{Velocity (in metres per second)} = 3.57 \sqrt{\frac{\text{percentage increase in volume per mm. of Hg increase of pressure.}}{}}$$

Or expressed in another way:

$$\text{Velocity (in metres per second)} = 3.57 \sqrt{\frac{\text{mm. of Hg rise of pressure required to produce 1 per cent. increase of volume.}}{}}$$

Thus a direct observation of the velocity of the pulse-wave, in any segment

¹ Working for the Medical Research Council.

of an arterial trunk, enables one to calculate, in absolute units, the mean extensibility of the vessels composing that segment.

II. *The Measurement of Pulse-wave Velocity.*

(a) *Historical.* The true nature of the pulse-wave was first recognized, and its velocity measured, by Weber (32) in 1834. Later, the subject was critically studied by Marey (19). Having shown that the delay which elapsed between the cardiac impulse and the arrival of the pulse-wave in different parts of the arterial system depended on the distance of any particular artery from the heart, he experimented with an artificial schema, in order to explain the reason for variations which he met with in the course of his observations on living animals. By this means he was able to vary at will, and independently of one another, the pressure and the density of the fluid employed, as well as the rate of flow through the vessels of which his model was composed. Further researches, both from a physiological and from a pathological standpoint, were made by François Franck (9), Waller (31), Rivals (25), and others; but the results obtained by many of the earlier observers are compromised by the fact that they measured the interval which elapses between the occurrence of the cardiac impulse and the arterial pulse, and made no allowance for the period of isometric ventricular contraction, which is subject to considerable variation. More recently, Münzer (21) has called attention to the great increase in pulse-wave velocity which is met with in cases of arterio-sclerosis. Friberger (10) investigated the relationship of pulse-wave velocity to age, and the following figures are given in his paper:

From 16 to 25 years	velocity	=	8.2	metres	per	sec.
" 25 " 36 "	"	"	9.4	"	"	"
" 45 " 55 "	"	"	9.4	"	"	"
above 55 "	"	"	10	"	"	"

He also showed that in chronic interstitial nephritis the mean velocity is considerably higher than in normal subjects.

Ruschke (27) studied the variations of pulse-wave velocity in various pathological conditions, as well as the modifications produced by the administration of drugs, and other therapeutic measures.

In two recent papers (14) Laubry, Mougeot, and Giroux, from observations on twenty normal young subjects, come to the following conclusions: (a) That the pulse velocity, expressed in metres per second, is approximately equal to the diastolic, or to half the systolic pressure, expressed in centimetres of mercury; (b) that the mean velocity in the lower limb is about the same as in the upper limb; and (c) that the velocity in the aorta is distinctly higher than in the limbs. They also give the results of a considerable number of observations in disease. Their results differ from those of Bazett and Dreyer (1), in which the velocity recorded in the smaller arteries was much higher than that in the larger vessels. If the results of Bazett and Dreyer be confirmed by further observations, they will necessarily lead to the conclusion, which is

in accordance with the histological evidence, that in health the smaller arteries are relatively less elastic than the larger ones.

(b) *The hot wire sphygmograph.* Most of the instruments which have been used for the purpose of investigating the velocity of transmission of the pulse-wave exhibit certain mechanical weaknesses. In the case of writing levers, for example, not only is it impossible to abolish lag, due to inertia of the system which varies in different instruments, but also the slowness of movement tends to round off the deflexions and, in rapidly travelling records, renders it extremely difficult to determine the precise commencement of the upstrokes. For this reason some workers (1) (15) (27) have used optical recorders, by which means both the weight due to the lever and the friction on the writing surface can be eliminated. But, even so, the restraint of the elastic membranes and the natural period of the instrument have to be taken into account. From a mechanical standpoint, therefore, the hot wire sphygmograph possesses certain advantages over other instruments, since lag and inertia are almost entirely abolished, while records obtained with a sensitive galvanometer yield deflexions the commencement of which is very clearly defined.

The instrument, which has been described in detail elsewhere (5), was designed by A. V. Hill. It is a modification of the Tucker hot wire microphone (30) which was employed during the war as a sound detector for locating enemy guns. It consists of a spiral of very fine platinum wire heated almost to redness by a current from a battery, and contained in a tube open at both ends. The hot wire and a dial resistance form two arms of a Wheatstone's bridge, which is connected to a string galvanometer. The other two arms of the bridge can be balanced in such a way that, when the instrument is at rest, no current is flowing in the galvanometer circuit. When, however, a puff of air passes through the tube the wire is cooled, its electrical resistance is altered, the bridge is thrown out of balance, and a current flows in the galvanometer. By connecting one end of the hot wire container to a suitable receiver, pulsations of the arteries may be made to produce in the tube pulsations of air capable of cooling the wire, and so of causing deflexions in the galvanometer.

The most convenient forms of receiver are, in the case of the carotid, a shallow cup such as is used with the clinical polygraph, and, in the case of the limb arteries, a plethysmographic bandage.

In hot wire records the primary deflexion of the galvanometer (with which alone we are concerned in the present paper) corresponds to the transmitted rise in pressure occurring at the moment when the pulse-wave enters the artery under the receiver; and, as soon as this rapid rise of pressure is over, the galvanometer returns rapidly to its zero position.²

(c) *Measurement of velocity by means of the hot wire.* If records be obtained from two points on an artery separated by a known distance from one another, the mean velocity with which the pulse-wave is travelling along that artery may be calculated.

² Under certain pathological conditions the normal form of curve is somewhat modified (7).

It is not practicable to place receivers on two different parts of the same artery, since the pressure of the proximal receiver will influence the time taken by the pulse-wave to reach the more distal parts of the vessel. It is best, therefore, to compare points on opposite limbs, first having ascertained what time-difference (if any) exists between corresponding points on the two limbs. In the case of the upper limb, one receiver may be applied to the right carotid artery and the other to the right radial. For, since these two vessels arise from a common trunk at the level of the sterno-clavicular joint, the distance travelled by the pulse-wave, in the time which elapses between carotid and radial deflexions, will correspond to the difference between the measurements from the sterno-clavicular joint to the receivers on the wrist and neck respectively.

Table I shows the mean velocities recorded in the upper limb in a series of twenty-two healthy young adults between the ages of 17 and 21. It will be seen that the results obtained by this method, in different individuals, differ but little from one another.

TABLE I.

Case.	Age.	Time Interval (in sec.).	Distance (in cm.).	Velocity (metres per sec.).
51	17	0.0904	48.5	5.4
54	17	0.0858	50	5.8
47	17	0.0864	51	5.9
72	17	0.0905	54	6.0
56	17	0.0849	53	6.25
11	18	0.0738	46	6.25
55	18	0.0912	56.5	6.2
76	18	0.0922	56.5	6.1
53	18	0.0883	50	5.7
15	18	0.0821	45.5	5.5
74	19	0.0884	53	6.0
4	19	0.0876	52	5.9
16	19	0.0859	50.5	5.9
6	19	0.0880	56	6.4
52	19	0.0869	56	6.45
9	19	0.0800	53	6.6
18	20	0.0923	53.5	5.8
12	20	0.0743	42.5	5.7
70	21	0.0884	51.5	5.8
19	21	0.0943	54	5.75
60	21	0.0860	51	5.9
5	21	0.0829	53	6.4

In this series, the velocities vary between 5.4 and 6.6 metres per second. In the majority (thirteen cases), the values lie between 5.8 and 6.3 metres per second, and of the remainder four give higher and five lower values. The time intervals in column 3 each represent the mean of three readings. Those records in which two of the time intervals differed from one another by more than 5 per cent. were discarded. It will be seen that the greatest deviation from the mean value of 6 metres is only about 10 per cent.

(d) *Pulse-wave velocity in isolated arteries.* In order to check the results obtained in living subjects, it appeared desirable to make a series of experiments with a view to determining directly the velocity of transmission of the pulse-

wave in an isolated human artery. For this purpose an artery without branches is most suitable, since the introduction of ligature material for tying off side branches might interfere, to some extent, with the natural elastic properties of the arterial walls. The artery selected was the common carotid. This vessel is unfortunately comparatively short, and hence the time interval available for measurement is very small. But, since the velocity of the pulse-wave is inversely proportional to the square root of the density of the fluid in the vessel, this difficulty may be partly overcome by replacing the blood with mercury. The density of blood being 1.055 and that of mercury 13.5, by using mercury the velocity will be decreased in the ratio of $\sqrt{13.5/1.055}$; that is to say, the time interval to be measured will be increased 3.58 times. By this means it is possible to measure the velocity, in an isolated artery, with considerable accuracy.

The artery is tied between the ends of two rigid metal pipes each of which is joined by means of rubber tubing to a glass reservoir. The distance between the ends of the pipes can be varied as required, each being clamped separately to a common support. The whole apparatus is filled with mercury, care being taken to drive out any air bubbles which may be present. Then, by striking one of the rubber tubes with the clenched fist, a wave may be transmitted through the artery. The pressure in the vessel is varied as required by raising or lowering the mercury reservoir. The height of the mercury in the reservoir above that of the artery (i.e. the pressure in the artery) is read off on a manometer scale.

The time of arrival of the wave is recorded at a given point in each of the metal tubes. In the original instrument described by Bramwell and Hill (3) the arrival of the wave was recorded by a light lever resting on a small piece of rubber membrane covering a window in the metal pipe. In an improved model, made and largely designed by Mr. A. C. Downing, of the Physiological Laboratory, the lever has been replaced by a hot wire which is activated by a rubber membrane closing a side branch of the metal tube. This modification yields much sharper deflexions, the record leaving its base-line so rapidly that measurements may easily be made with an accuracy of about 0.0003 sec.

The results of these experiments, which have been published in detail elsewhere (2), show (a) that, at pressures similar to the diastolic pressure in man, the pulse-wave velocity approximates closely to the values obtained in observations made with the hot wire sphygmograph in living subjects, (b) that the velocity in arteries from old people is higher than in those from young people, and (c) that at high pressures the velocities are very much higher than at low pressures.

III. *The Influence of Pressure on Arterial Elasticity.*

The elasticity of an artery, in the living body, depends not only on the structural constitution of the arterial wall, but also on the functional conditions

to which it is subject at the moment. Of the latter probably the most important³ is the pressure of the blood within the artery.

(a) *Clinical sphygmograms.* From a qualitative standpoint, the variation of arterial elasticity with pressure is well illustrated by simple clinical sphygmograms. Excluding such extraneous factors as inaccessibility of the radial artery owing to the condition of the intervening tissues, the amplitude of the percussion wave in a record obtained with Dudgeon's sphygmograph depends on two factors:⁴ the pulse-pressure, and the initial tension of the arterial walls.

A vessel, the wall of which is still under considerable tension at the end of diastole, will expand very little with the increased pressure of systole, even though the pulse-pressure (i.e. the difference between systolic and diastolic pressures) be high; whereas a vessel, the wall of which is relatively relaxed when the pulse-wave arrives, will require but a small increase of pressure to produce a considerable excursion. The condition *par excellence* in which arteriograms of large amplitude are obtained is advanced aortic incompetence, associated with a powerful left ventricle. That this is due largely to the low initial tension of the arterial wall is evident from comparison with records obtained from cases of chronic interstitial nephritis. In the latter disease the pulse pressure may be as high as in the former; but, since the diastolic pressure is also raised (instead of lowered), the arterial wall is functionally inelastic, and the amplitude of the sphygmogram is small. These facts may be represented diagrammatically by what has been termed the 'absolute sphygmogram' (11).

(b) *Observations on isolated arteries.* From a quantitative standpoint, the relationship of elasticity to blood-pressure may conveniently be studied in isolated arteries. Such observations are open to two criticisms, (a) that arteries removed at autopsy come from pathological subjects, and (b) that they may have undergone some degree of post-mortem change. But in a series of experiments, the results of which have been published elsewhere (2), Bramwell, Downing, and Hill found that vessels taken from patients in whom there was no gross evidence of arterial disease exhibited a very constant relationship between elasticity and pressure. The curve relating elasticity to pressure appears, as might be expected, in its most characteristic form in observations made on arteries obtained from young people. Fig. 1 shows diagrammatically the results of a typical experiment on a child aged 8, pulse-wave velocity being plotted against pressure. The actual figures from which this curve was plotted are given in Table II.

It will be seen that, at low pressures, the velocity remains fairly constant; but, as the internal pressure rises above the normal diastolic value, it rapidly

³ In the case of the larger arteries, at any rate, it is improbable that the small amount of muscular tissue present can exert any considerable influence at such pressures as are normally prevalent during life. This subject is at present being investigated, and will be considered in a subsequent paper.

⁴ The suddenness of change of pressure also influences the form of the record, but this is partly due to overthrow, attributable to mechanical defects in the instrument.

increases. If instead of velocity we plot elasticity, which may be calculated from the formula given above (p. 225), and which is inversely proportional to the square of the velocity, the effect of pressure becomes even more evident. The actual pressures to which an artery is subject during life lie on that part of the curve where the ascent is steepest. Hence a very small displacement to the right, indicating but a slight rise in diastolic pressure, will signify a con-

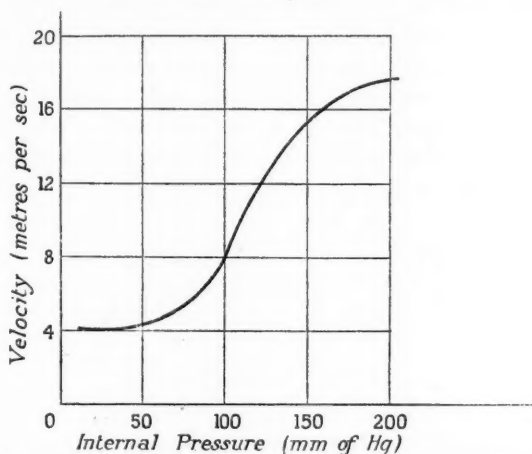


FIG. 1. Curve showing relation of pulse-wave velocity to internal pressure, from observations on the common carotid artery of a child of eight.

TABLE II.

Pressure mm. of Hg.	Observed Interval (sec.).	Velocity in Hg (metres per sec.).	Calculated Velocity in Blood (metres per sec.).
15	0.0407	1.15	4.12
15	0.0414	1.13	4.05
20	0.0392	1.19	4.26
45	0.0380	1.23	4.40
60	0.0351	1.33	4.76
75	0.0330	1.41	5.05
90	0.0270	1.73	6.20
105	0.0199	2.35	8.43
120	0.0145	3.22	11.53
140	0.0123	3.8	13.6
170	0.0099	4.7	16.8
200	0.0095	4.9	17.5

siderable diminution in arterial elasticity, and a correspondingly great increase in the amount of energy which the heart is called upon to expend in maintaining its output. These facts will receive further consideration below.

(c) *Observations on a case of cardiac arrhythmia.* The variation of pulse-wave velocity with pressure may be observed, during life, in certain cases of cardiac irregularity. Pl. 17, Fig. 2 is taken from a patient who exhibited sino-auricular block (Fig. 3). The time intervals between the carotid and radial upstrokes in six cycles, as measured by means of a Lucas comparator (18) (16), are shown in the following table:

TABLE III.

Cycle.	Time Interval in secs.	Calculated Velocity in metres per sec.
1	0.080	6.6
2	\times 0.091	5.8
3	0.082	6.5
4	0.080	6.6
5	0.079	6.7
6	\times 0.089	6.0

Here the average time interval in the four cycles following a short diastole is 0.080 seconds, whereas the average in the two cycles following a long diastole (\times) is 0.090 seconds. Since it is only reasonable to assume that other conditions remained constant, this can best be accounted for by the fact that during the longer pauses the diastolic pressure had time to fall to a lower level than during the shorter ones.

(d) *Observations on 'effective pressure' in living subjects.* The experiments on isolated arteries showed that variations in internal pressure exert an important influence on arterial elasticity; it seemed desirable, therefore, to devise a method of investigating this relationship in the living subject. The variations in diastolic pressure which can be produced by the administration of drugs, by local applications of heat and cold, and by other physical means are difficult to control, and for this reason the following method, which has been described in detail by Bramwell, McDowall, and McSwiney (6), was employed:

A portion of the arm is enclosed in a sphygmomanometer bandage of known width, and a series of pulse-wave velocity observations are made with different pressures in the armlet. Now if the pressure in the armlet be p , then the 'effective pressure' stretching that portion of the artery which is under the armlet will not be P , the diastolic pressure, but $(P-p)$. In this way the velocity of the pulse-wave in the segment of the vessel under the armlet will be reduced, on account of the increased elasticity of the arterial wall, resulting from diminution of the effective pressure.

In a series of experiments (6) made in this way the curve relating velocity to 'effective pressure' over a range from zero up to the diastolic pressure was determined. It closely resembled in form the curve obtained, over the same range of pressures, in the case of isolated arteries.

(e) *The relationship of arterial elasticity to diastolic pressure.* The results referred to above can best be explained on the hypothesis that the arterial wall differs from a simple rubber tube in consisting of two elements, one of which is elastic and the other relatively non-elastic. When the wall is stretched the non-elastic element comes into play; and, once stretching has proceeded to any considerable extent, the influence of the elastic element, for the time being, becomes relatively insignificant. Hence a normal healthy artery is much more elastic at low than at high pressures. In experiments on isolated arteries, the curve (Fig. 1) relating pulse-wave velocity (which is a function of elasticity) to pressure exhibits a very characteristic form. At low pressures the artery is

extremely elastic and pulse-wave velocity increases only very gradually as the pressure rises; at high pressures, on the other hand, the velocity increases much more rapidly, since the artery has become relatively non-elastic.

In certain wasting diseases the elastic element of the arterial wall loses its efficiency, and hence throughout its whole course the pressure-elasticity curve is represented by a line which is almost straight, its characteristic form being entirely lost. An example of such a condition was cited in a paper by Roy (26), the artery in question being obtained from an extremely emaciated dog; and very similar results have been obtained by Bramwell, Downing, and Hill (2), in man. In such arteries, at low pressures, the increase in volume for a given

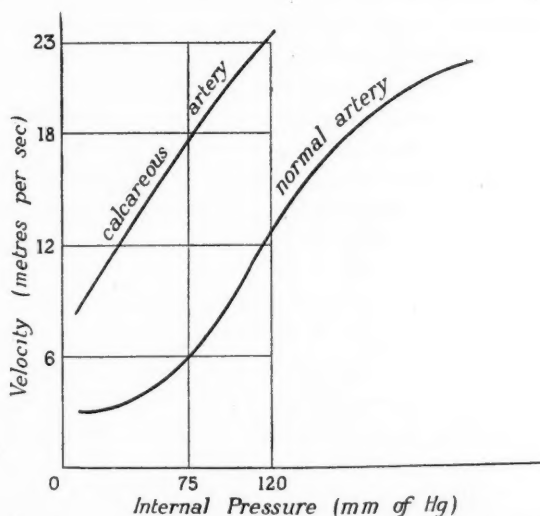


FIG. 4. Curve showing the abnormal relation of pulse-wave velocity to internal pressure which was observed in an artery exhibiting very marked calcification of the tunica media. A curve from an artery of a 'normal' adult is given for purposes of comparison. Taking 75 mm. Hg as an average value for the normal diastolic pressure, the healthy artery gives a velocity of 6 metres per sec., while the calcareous vessel gives a velocity of 17 metres per sec.

increase in pressure is much less than in normal healthy arteries; but at high pressures, since the elastic element of the normal artery is working at a disadvantage, the difference is less obvious.

In calcareous arteries, on the other hand, the stiffening of the vessel wall is attributable, not merely to a loss in efficiency of the elastic element, but to the deposition of new material which is non-elastic. A calcareous vessel differs from one which has merely lost its elasticity in that, even at low pressures, the former is much less elastic than the latter, the whole curve relating velocity to pressure being not only flattened out but displaced upwards (Fig. 4). Hence, during life, the pulse-wave velocity in a stiffened artery, even at a low pressure, is much higher than that in a normal artery at the normal diastolic pressure.

The results obtained by Roy (26) in his experiments on the extensibility of

isolated arteries from animals are in general agreement with the present series of observations in the human subject. From his figures Bramwell and Hill (3) have shown that, in the case of healthy animals, a rise of pressure up to about 80 mm. Hg caused relatively little increase in the velocity of transmission of the pulse-wave, but that above this point pressure and velocity exhibited a direct relationship to one another. That is to say, the curve relating velocity to pressure tends to rise steeply as soon as the non-elastic element comes into play.

Dawson (8), who investigated the effect of variations in blood-pressure on pulse-wave velocity in dogs, was unable to find any constant relationship between the two. The discrepancy of his results can probably be explained by the fact that he relied on nervous stimulation to produce variations in blood-pressure, and that the variations in pulse-wave velocity which he observed were due not merely to variations in pressure, but also to other complicating factors which are difficult to control in the living animal.

If the normal range of variation in diastolic pressures in healthy adults be taken as lying between 60 and 100 mm., it will be seen that it is in the upper part of this range that the experimental curve of pulse-wave velocity from a healthy artery is rising most steeply. Hence, quite a small rise of diastolic pressure is sufficient to produce a very considerable diminution in arterial elasticity.

Between the pressures of 75 and 120 mm. the two curves in Fig. 4 are almost parallel to one another. If, however, pressure were plotted against elasticity, instead of against velocity, this would not be the case, since elasticity varies inversely with the square of velocity. In the stiffened artery, therefore, the diminution in elasticity over this range of pressure is very much greater than in the healthy artery.

(f) *The effects of high diastolic pressure.* In order that an artery may attain its highest functional efficiency it is desirable that the range of pressures in which it is working should be sufficiently low to allow the elastic element to come into play. The relationship of blood-pressure to arterial elasticity is one of great practical importance in disease. The higher the diastolic pressure the less elastic will be the arteries, and the more work will the heart be called upon to perform. The percentage increase in volume of the arteries, for example, with a rise of pressure from 80 to 120 mm. is very much greater than with a rise from 120 to 160 mm. Conversely, considering the recoil of the arteries from their distended to their resting state, the higher the diastolic pressure the higher must be the pulse-pressure to enable a given volume of blood to be passed on to the capillary area; the output with a fall of pressure from 160 to 120 being much smaller than with a fall from 120 to 80 mm. The following comparison will make this point clear:

Case I. Male, 72 years of age, suffering from complete heart-block. Blood-pressure 190/80. The superficial arteries exhibited an extreme degree of calcification.

Case II. Female, 23 years of age, suffering from chronic interstitial

nephritis. Blood-pressure 220/140. The walls of the superficial arteries did not present any obvious abnormality.

In both these cases the mean velocity of the pulse-wave from carotid to radial was 11 metres per second. In other words, an apparently healthy artery at an effective pressure of 140 mm. was just as inefficient as an extremely stiffened artery at an effective pressure of 80 mm.

These two cases are typical examples of what might be called the anatomical and the physiological types of arterial inefficiency. In either type the impairment of arterial elasticity is, by itself alone, sufficient to limit the physical capacity of the patient. Regarding the same problem from another aspect, Bramwell, Downing, and Hill (2) have shown that in an isolated artery, at low diastolic pressures, a very small pulse-pressure is sufficient to produce a considerable increase in the volume of the artery; but that when the diastolic pressure is high, even an extremely high pulse-pressure produces but little alteration in the arterial volume. Now if we assume, as it seems reasonable to assume, that the general relationship, during life, between arterial volume and pressure in the aorta and other great vessels is comparable to that which has been demonstrated in isolated arteries, it is obvious that at high diastolic pressures, even with an increased pulse-pressure, the arteries are only capable of accepting a very small ventricular output. So that, even with a rapid heart-rate, the oxygen supply to the tissues would only be sufficient to meet the demands of very limited muscular activity.

IV. *The Variation of Arterial Elasticity with Age.*

In a series of 74 normal individuals of ages ranging from 4 up to 84, investigated by Bramwell, Hill, and McSwiney (5), it was shown that pulse-wave velocity increased progressively with age.

It is necessary further to define what is meant by 'normal healthy individuals'. For the purpose of this investigation it has been taken to mean those who fulfil the two following conditions: (a) That their present state of health should be such as to enable them to meet the ordinary requirements of life, and (b) that careful inquiry should reveal either no history of serious illness in the past, or, in the event of past illness, subsequent athletic achievements sufficient to exclude all probability of permanent cardio-vascular damage.

In the case of members of the upper and middle classes of society, the conditions under which we live at the present time make very little demand upon the cardio-vascular system. Consequently it is usual to consider those individuals who are able to carry on more or less sedentary occupations without signs of functional insufficiency, cardiac or otherwise, as members of the normal healthy group. With the labouring classes, however, this is not so, for, in their case, the physical exertion to which they are subject makes a greater demand upon the reserve power of the heart, and the man whose heart is unable to meet that demand soon passes from the category of the normal into that of the unfit.

These facts were clearly brought home during the war, when it was found that many of the recruits drawn from the sedentary walks of life soon develop the 'effort syndrome', when subjected to the more strenuous physical conditions of the training camp (17). It would therefore appear to be justifiable to make a further subdivision of the 'normal healthy class' into (a) those who are distinctly above the average and of an athletic type, (b) those who are distinctly below the average and of a sedentary type, and (c) an intermediate average normal group. The mean curve relating pulse-wave velocity to age might be expected to pass through the observations made on individuals belonging to the average normal type, whereas those from athletes, whose pulse-wave velocity is relatively low for their age, would tend to fall below the line, and those from sedentary individuals whose arteries are relatively stiff, and whose pulse velocity is higher than normal, would tend to fall above the line.

The group investigated by Bramwell, Hill, and McSwiney consisted largely of schoolboys and university students, but also included laboratory assistants, builders' labourers, and others. The values recorded in 74 subjects ranged from 4.7 to 8.6 metres per second. Further, it was shown that, amongst young individuals at any rate, the deviation from the mean value was less than ± 1 metre per second. So far as these observations went, they tended to show that the same relation held good for the more advanced ages, but the number of observations on older subjects was too small to warrant any definite deductions regarding the limits of variation.

Above the age of 60 it is more difficult to define normality, so far as the arteries are concerned; for, whereas the average man or woman in the sixth and seventh decades may be perfectly capable of meeting the requirements of a somewhat restricted activity, there are exceptional individuals of this age whose physical powers are retained to quite a remarkable extent. At first sight, one is tempted to regard the latter as 'normal' healthy people, but it would probably be more correct to regard them as abnormal, in the same sense that an athlete may be regarded as deviating from the mean normal standard. Normality must necessarily be defined as an approximation to the average, and from this aspect it is not justifiable to regard an old man with young arteries as being any more normal than a young man with old ones.

From Table IV, which gives the ages, diastolic pressures (as estimated by auscultation), and pulse-wave velocities of some of the subjects referred to above, it is evident that the variations in pulse-wave velocity cannot be accounted for merely by variations in the diastolic blood-pressure.⁵ The same conclusion is indicated by the observations of Bramwell, Downing, and Hill (2) on isolated arteries. They have shown that, in arteries removed *post mortem* from subjects in whom there was no gross evidence of arterial disease, there exists the same general relation between age and pulse-wave velocity as in living subjects.

⁵ All the observations on pulse-wave velocity referred to in this paper have been made at the diastolic pressure, on account of the fact that the front of the pulse-wave presents the greatest facilities for accurate measurement.

The relationship of pulse-wave velocity to age is dependent on two factors—the structural condition of the arterial wall, and the pressure to which it is subjected. In children the blood-pressure is low and the arteries are extremely elastic; in adults the blood-pressure is higher and the arterial walls are less elastic. In the case of old people, however, although the systolic pressure continues to rise, the diastolic according to most observers (12) (29) (35) shows little or no tendency to do so, but owing to the loss of arterial elasticity, pressure for pressure, the pulse-wave velocity is higher in old than in young subjects.

To sum up, the diminution in arterial elasticity which is associated with advancing years will so modify the normal relationship between pressure and pulse-wave velocity as to give lower velocities in children, and higher velocities in old people, than would the corresponding pressures in the case of a healthy isolated artery obtained from a young adult.

TABLE IV.

Showing Pulse-wave Velocity in eleven subjects in whom the Diastolic Pressure was between 60 and 70 mm.

No.	Age.	Diastolic Pressure (mm.).	Velocity (metres per sec.).
5	21	70	6.4
6	19	60	6.4
13	28	70	6.7
14	11	65	4.7
15	18	70	5.5
18	20	65	5.8
29	84	60	8.6
47	17	65	5.9
49	15	70	6.1
53	18	60	5.7
69	29	70	6.9

The relatively low diastolic pressure in old age makes up to some extent for the loss in elasticity, by allowing the stiffened arteries to work over a range where the elasticity is greater than it would be at higher pressures. But owing to the steepness with which the pressure-elasticity curve descends in stiffened arteries, it is further necessary that the pulse-pressure should be very considerably increased, to enable the arteries to accept a ventricular output sufficient to meet the requirements of the tissues.

V. *Pulse-wave Velocity in Disease.*

From previous observations (4) it is evident that, under pathological conditions, the velocity of the pulse-wave may attain values far beyond the normal limits of variation which are met with in health. But, until the different factors upon which these variations depend have been more fully investigated, it does not appear justifiable to attempt to draw any conclusions regarding the actual values recorded in different diseases. Many of the deductions which have been made from observations on pulse-wave velocity in disease are of little value, owing to

the fact that cases have been grouped together purely on account of their clinical or pathological relationships; whereas, from a physiological standpoint, they may exhibit features which would necessitate quite a different classification. Unless, therefore, great discrimination be exercised in the grouping of cases, the results obtained will serve to obscure rather than to elucidate the issue.

As pointed out above (p. 232), in the living body the elasticity of the arterial walls at any given moment depends not only upon their structure, but also upon the 'effective pressure' to which they are subjected. The latter factor is varying continually throughout the cardiac cycle, the limits of variation depending on the systolic and diastolic pressures. The time relations of the change of intra-arterial pressure, as shown by the form of the pulse-curve, may prove to be of value in classifying pathological cases from this standpoint.

In observations made on isolated arteries, on the other hand, such complicating factors as the effective pressure are directly under control. Hence experiments of this kind yield more definite information concerning the influence on elasticity of structural changes in the arterial wall, the interpretation of results obtained being much less liable to error. It has, therefore, been considered advisable to concentrate attention on this aspect of the subject before proceeding to investigate the much more complicated problem of the pathological variation of pulse-wave velocity in living man. Having ascertained the normal relationship between age and elasticity on the one hand, and between pressure and elasticity on the other, and further having defined the limits of variation which are met with in health, the task of investigating the modifications of arterial function occurring in disease will be very much simplified.

VI. *Some Theoretical Considerations*

(a) *Arterial function.* In the present paper no attempt has been made to consider the important question of localized arterial disease, affecting the vessels supplying vital organs such as the brain and heart. Attention has been devoted solely to the influence of arterial elasticity on the circulatory mechanism as a whole. For, in addition to their function as delivery tubes, the aorta and great arteries must be regarded as elastic reservoirs, the purpose of which is to relieve the strain on the heart and to prevent sudden changes of pressure in the peripheral arteries.

At each ventricular systole a certain volume of blood is thrown suddenly into the aorta. This necessitates either (a) a corresponding displacement of blood to the periphery, or (b) a temporary increase in the capacity of the aortic chamber: the greater the distensibility of the aorta, the smaller will be the volume of blood which has to be displaced. The energy developed by ventricular systole may, therefore, be utilized in two ways, namely, (a) in producing an actual forward movement of the blood column in the arteries, and (b) in stretching the aortic (and arterial) walls. The extent to which each of these processes participates in

enabling the aorta to accept the ventricular output depends on the resistance of the respective forces to which each is opposed. But since the healthy aorta is highly elastic, and since resistance to forward movement of the blood column is considerable, a force which produces but little forward movement in the blood column will be sufficient to cause considerable distension of the aorta. Hence, during the initial phase of systole, it is distension of the aorta, rather than displacement of the blood which it contains, that plays the more important part in accommodating the ventricular output. Thus the energy generated in the left ventricle is utilized largely in distending the aorta, being converted into potential energy in the stretched aortic wall.

Poirier (22) has pointed out that the diminution in calibre of the arch of the aorta throughout its course is not proportional to the size of the branches which arise from it; and Sainsbury (28) and others have emphasized the fact that its calibre is excessively large as compared with the capacity of the left ventricle. If the sole function of the aorta were to act as a simple delivery tube, a very much smaller calibre would suffice to meet the requirements of the heart, and this apparent discrepancy is accounted for by the fact that the aorta is not merely a delivery tube, but an elastic reservoir, the purpose of which is to relieve the strain on the heart, and to prevent sudden changes of pressure in the peripheral arteries.

(b) *Arterial elasticity and the work of the heart.* By means of optical records of the pressure changes in auricle, ventricle, and aorta, Wiggers (33) (34) has been able to measure with accuracy, in animals, the duration of the different phases of the cardiac cycle. His observations show that the pressure in the aorta is rising only during the earlier part of the ejection phase of ventricular systole. And since at rest, when the heart is acting quietly, the total duration of this phase is only about one-third of the whole cardiac cycle, it is evident that the stretching of the aorta takes place very rapidly as compared with its subsequent collapse. What has been said of the aorta applies to all arteries of the body. The phase of arterial distension occupies but a small fraction of the whole cardiac cycle, and the time available for any particular vessel to pass on its contents to the periphery is considerable, as compared with that occupied in dilating to receive them. Each segment of the arterial tree helps to reduce the distension of the segment proximal to it (and so ultimately the effort of the heart) by providing, in response to a relatively small rise of pressure, temporary accommodation, at short notice, for a considerable volume of blood, the disposal of which to the periphery can proceed throughout the whole of the long period of arterial retraction. Regarded from this standpoint, the efficiency of arteries depends solely on their elasticity. The greater the elasticity of the arteries, the lower will be the pressure required to produce a given increase in their volume. And, since the energy expended by the heart per beat has been shown to be proportional to the pressure developed (23) (24), the effort which it is called upon to make in expelling its contents will vary inversely with the elasticity of the arterial walls.

(c) *Arterial elasticity and the capillary circulation.* In addition to helping

to reduce the work of the heart, the elasticity of the arteries is of great importance from its influence on the capillary circulation. The capillary area has been aptly described as that part of the body in which 'the essential business of life' is carried on. That this business should be carried on with the highest possible efficiency, under ever-varying conditions, is the fundamental purpose of the whole circulatory mechanism, the heart and vessels being entirely subservient to this one object. An efficient capillary circulation implies that a certain volume of blood shall pass through the capillary area in unit time, and at a certain rate. If the quantity of blood be inadequate to meet the requirements of the tissues, anoxaemia will result; if it be excessive the heart will be called upon to do unnecessary work. Secondly, for a given blood-flow per minute, the more uniform the capillary rate the greater will be the volume of oxygen available for the tissues.⁶ Such uniformity necessitates an arterial pressure which is relatively constant throughout the cardiac cycle, or, in other words, a low pulse-pressure. It is in relation to the pulse-pressure that the importance of arterial elasticity is most evident. As has been shown above, other things being equal, the more elastic the arteries the lower will be the systolic pressure required to produce a given increase in their volume. Similarly, during the phase of arterial retraction, the more elastic the arteries the smaller will be the fall of pressure for a given decrease in volume. In other words, the more elastic the arterial walls the lower will be the pulse-pressure, and the more uniform the blood-flow through the capillaries.

Thus, both from the point of view of the heart and of the capillary circulation, the greater the alteration in the volume of the arteries in response to a given alteration in pressure the more efficient will be the arterial mechanism. This alteration in volume is shared between the various arteries of the body, the larger arteries providing a greater absolute expansion than the smaller ones; it is natural, therefore, to conclude that a given artery provides its share in the elastic expansion better, the greater be its change in volume for a given rise or fall of pressure.

The relative proportion of the elastic and muscular elements of the arterial wall varies considerably in different vessels, and from an anatomical standpoint the arteries have been classified by Jaques (13) in two main groups: (a) those of the 'elastic type', such as the aorta, subclavian, and carotid, and (b) those of the 'muscular type', such as the radial and lingual. Medium-sized vessels such as the axillary and common iliac are transitional in structure between these two types. It is therefore not surprising that physiological evidence (1) should have been brought forward to show that, under normal conditions, the smaller arteries are relatively less elastic than the larger ones. If this be the case, disease of the aorta and of the main arterial trunks will, from the point of view of

⁶ To illustrate this, imagine that 1 c.c. of blood has 70 per cent. of its oxygen taken out of it in passing through a given capillary at a uniform speed. If half of it were to pass very slowly perhaps 80 per cent. might be taken out, while the other half passing very rapidly might lose 30 per cent., so that on the whole only 55 per cent. of the oxygen would be lost instead of 70 per cent.

elasticity,⁷ be of much greater importance than corresponding changes in the smaller vessels.

VII. *Summary and Conclusions.*

1. An instrument is described by means of which pulsations on the surface of the body can be recorded with a string galvanometer.

2. Preliminary observations showed that the hot wire sphygmograph, on account of its mechanical properties, was capable of recording the time of arrival of the pulse-wave at different points of the body with a high degree of accuracy. It appeared, therefore, to be extremely suitable for investigating the velocity of transmission of the pulse-wave.

3. The velocity of transmission of the pulse-wave is a measure of arterial elasticity, in accordance with the formula:

$$\text{Velocity (in metres per second)} = 3.57 / \sqrt{\frac{\text{percentage increase in volume per mm. of Hg increase of pressure.}}{}}$$

4. The variations observed in pulse-wave velocity show that the elasticity of the arteries is affected to a very marked degree by different physiological and pathological conditions. The more perfect the elasticity of the arteries the greater is their change of volume for a given rise or fall of pressure. Hence from the point of view both of the heart and of the capillary circulation arterial elasticity is a factor of fundamental importance to the circulatory mechanism.

5. In a series of observations on 22 healthy young subjects the average velocity of the pulse-wave was found to be 6 metres per second.

6. A method of determining the pulse-wave velocity in short pieces of excised artery is described. The velocities recorded, at pressures corresponding to the normal diastolic pressure in man, agreed closely with, and so served to corroborate, the results obtained from observations on living subjects.

7. The influence of blood-pressure on arterial elasticity is discussed. This aspect of the problem was investigated by experiments on isolated human arteries, as well as on living subjects. Both methods gave similar results. It was found that at low pressures healthy arteries are extremely elastic, but that as the pressure rises above the normal diastolic value their elasticity rapidly diminishes. These facts point to the conclusion that in healthy young subjects during life the elasticity of the arteries is largely dependent on the diastolic pressure. The higher the diastolic pressure the less efficient will be the arteries, and the greater will be the energy required of the heart in ejecting its contents.

8. In disease, on the other hand, not only is the elasticity of the vessel wall impaired, but the characteristic relationship of elasticity to pressure, which exists in health, is no longer present.

Under pathological conditions loss of elasticity may be due either to

⁷ From the point of view of blood-supply to the vital organs, disease of the cerebral or coronary arteries is doubtless of primary importance.

a temporary functional cause (i. e. stretching of the arterial wall by a high blood-pressure) or to a permanent structural change. But, whatever the cause, it will be attended by far-reaching results, since even a considerable increase in pulse-pressure will enable the vessels to accept only a relatively small ventricular output. The raised pulse-pressure entails a corresponding increase of systolic pressure. This puts an additional strain upon the heart, and consequently imposes a limit on the oxygen intake, and on the amount of exertion which the individual is capable of undertaking.

9. In the past, attention has been concentrated largely on the way in which disease affecting special areas of the arterial field is likely to interfere with the blood-supply of individual vital organs. This aspect is no doubt of primary importance, but the quantitative results which have been obtained in the present investigation suggest that the more general consequences of variations in arterial elasticity, on the circulatory mechanism as a whole, are deserving of further investigation.

10. A method is described by means of which it is possible to determine in living man the actual elasticity of the arteries in the limbs at all 'effective pressures' between zero and diastolic. Since the most characteristic portion of curve relating elasticity to pressure lies in this region, absolute measurements of arterial elasticity obtained by this means are likely to yield valuable information concerning the functional efficiency of the arteries, under different pathological conditions. Until, however, a larger amount of pathological material has been studied the writer does not feel justified in drawing any general conclusions as to the functional efficiency of the arteries in disease: attention in the present paper has therefore been confined, almost entirely, to observations on normal subjects.

11. In a series of 74 healthy individuals of ages varying from 4 up to 84 it was found that pulse-wave velocity varied directly with age. Values ranging from 4.7 up to 8.6 metres per second were recorded. A similar relation was demonstrated in isolated arteries.

The limits of normal variation in the case of young subjects was found to be less than ± 1 metre per second; and similar observations are being made with a view to determining the limits of variation in older people. From the mean velocities obtained it can be shown that between the ages of 10 and 60 the elasticity of the arteries is halved. This relation between age and velocity suggests that the increase in systolic pressure, and in pulse-pressure, in accordance with age, is a compensatory mechanism designed to enable the heart to maintain its output in spite of the decrease in arterial elasticity which accompanies advancing years.

It is a pleasure to acknowledge the help which I have received throughout this work from my friend Professor A. V. Hill, whose personal co-operation and expert advice have proved invaluable to me. I am also indebted to Drs. B. A. McSwiney and R. J. S. McDowall, and to Mr. A. C. Downing, who have worked with me on different aspects of the problem; to Professor J. Shaw Dunn for the

facilities afforded me in obtaining the material on which are based the observations on isolated arteries; and to Drs. George R. Murray and E. M. Brockbank for permission to investigate the three cases referred to in the text.

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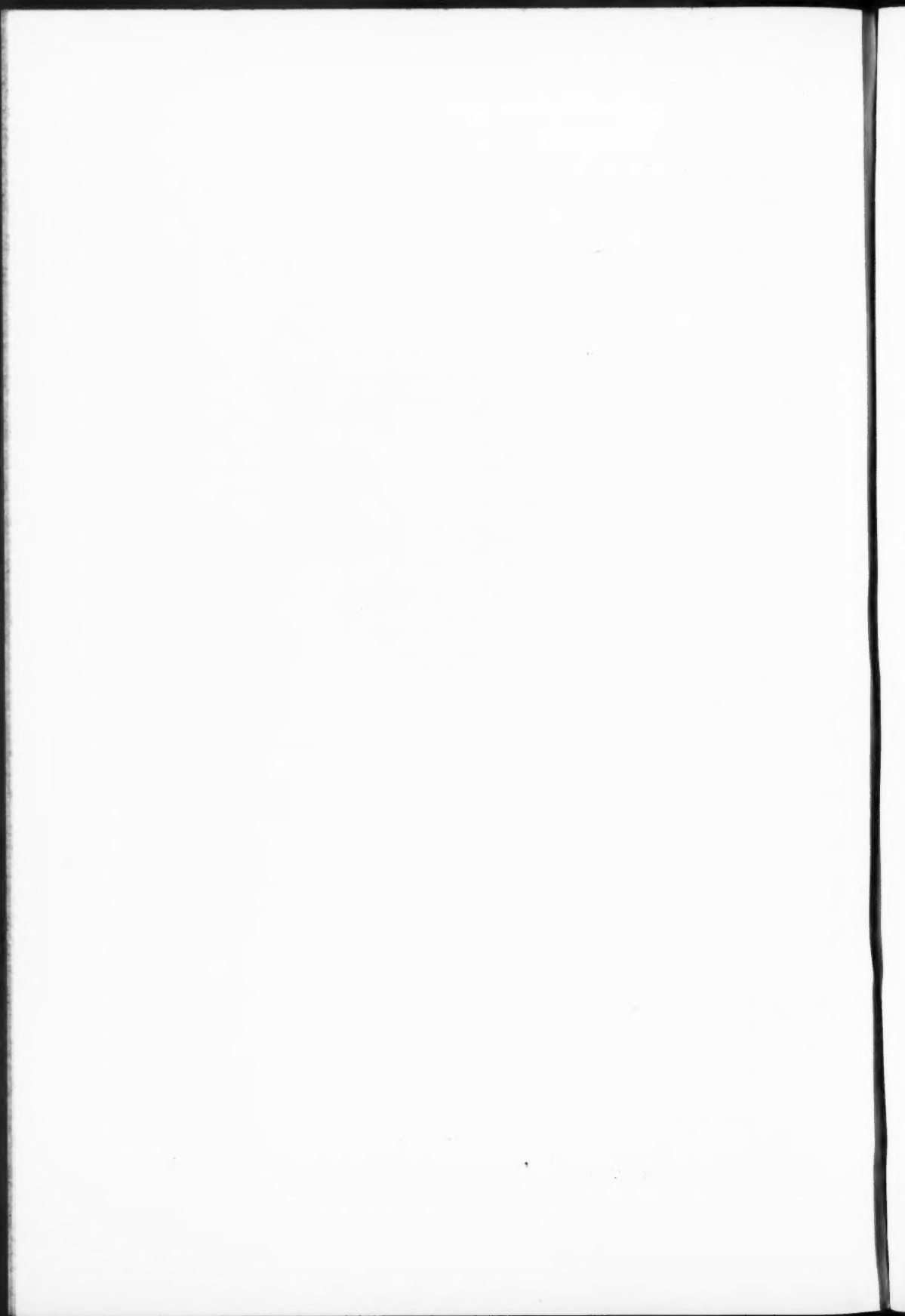
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DESCRIPTION OF FIGURES.

PLATE 17, FIG. 2. Simultaneous hot wire sphygmogram of carotid (c) and radial (r) pulses recorded on the same galvanometer string. Time intervals 0.2 sec.

FIG. 3. Electrocardiogram, lead II, from the same patient as Fig. 2, showing sino-auricular block. Time intervals 0.2 sec.



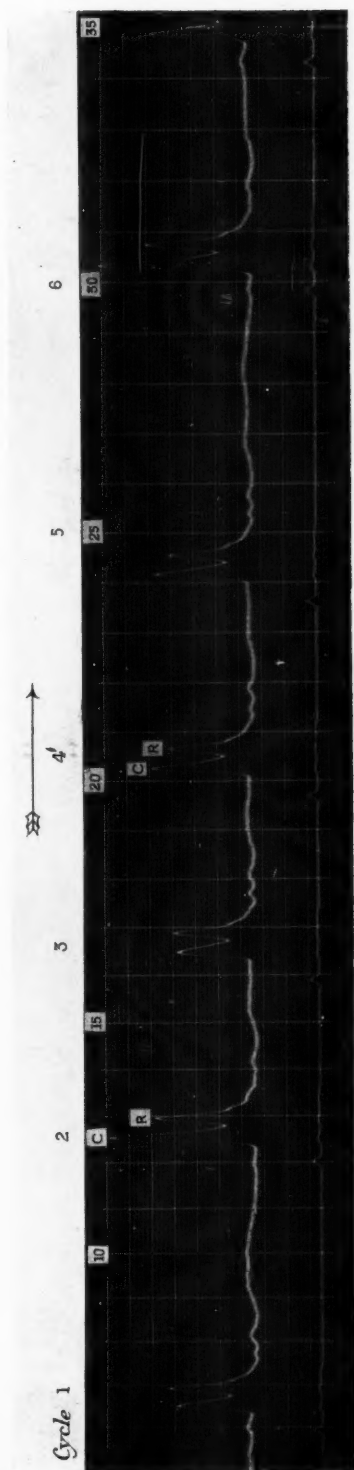


FIG. 2

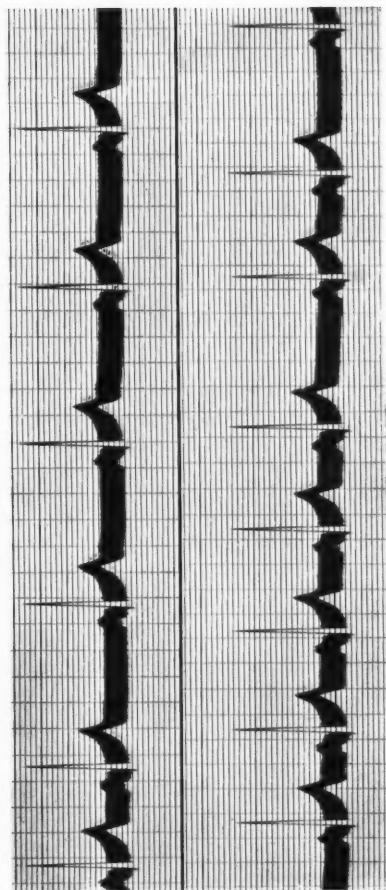


FIG. 3

STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM

PART III. THE ABSORPTION OF CALCIUM AND PHOSPHORUS AND THEIR FIXATION IN THE SKELETON

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Historical.

THE importance of the mineral content of the diet in nutrition, and particularly in relation to bone growth, has been recognized for many years. As far back as 1842, Chossat found that pigeons could not be reared on wheat alone; and when such a calcium-poor diet was maintained severe nutritional disturbance and finally death ensued. When calcium carbonate was added to the diet the birds remained healthy and their skeletons developed normally.

In the excellent compilation on phosphorus metabolism by Forbes and Keith (1) there is an exhaustive summary of the studies which have been made on the mineral elements of the diet as affecting skeletal growth. Much of the earlier work is of fundamental importance, and the results and conclusions would appear to deserve careful consideration at the present day, especially in view of the recent investigations in experimental rickets, and the causation of the disease in animals by modifications of the mineral content of the diet. A brief reference to this work will serve to indicate the importance of the mineral matter of the diet in the growth of bone.

Dusart in 1869 found a pigeon lost calcium phosphate from the skeleton as well as body-weight when fed on wheat alone. A food especially poor in calcium and phosphorus, or in calcium alone, was shown by Weiske, in experiments with milch-goats, to cause death before any noticeable changes in the bones were observed. This investigator noted that although the percentage of bone ash might vary, the composition of the ash remained almost constant.

In 1880 E. Voit found that the lack of lime in the diet caused a reduction of the phosphorus as well as of calcium in the bones of dogs. He and others determined that the bones of birds became poor in earthy salts and easily bent if the food was deficient in mineral matter. Henry found that the bones of pigs fed on corn increased in strength and in mineral matter when bone meal was

added to the diet. Rasquin fed two young cocks, one with and the other without powdered bone for 120 days. The weight of the skeleton per kilo of body-weight was in the former case 87.7 grm., in the latter 76.8 grm. Burnett (1906-1910) showed that hogs receiving additions of bone meal, calcium carbonate, or disodium phosphate to natural foods had bones greatly increased in breaking strength, specific gravity, thickness of wall, and ash content. Commenting on Burnett's results, Forbes and Keith remark: 'These tables . . . show more plainly than any of the earlier work the fact that the mineral content of the bones may be modified in accordance with the composition of the foods through a very wide range of variation.'

Additional stimulus to the study of the fixation of the bone-forming elements has been given by recent researches in experimental rickets. Sherman and Pappenheimer (2) and Shipley, Park, McCollum, and Simmonds (3) have shown independently that rachitic changes in the skeleton of rats may be induced by modifications of the mineral constituents of the diet alone. When the phosphorus content of the intake was reduced below a certain minimum, ossification was found to become abnormal and a rickets-like condition of the bones, indistinguishable from that produced by the disease developing spontaneously, finally resulted. Similar results were obtained when the diet was deficient in calcium though rich in phosphorus (4). It has also been shown by Elliot, Crichton, and Orr (5) that rickets which develops in young pigs can be cured and prevented by a simple adjustment of the mineral balance of the diet. It would seem, as one would naturally anticipate, that an insufficiency of one or other of the bone-forming elements in the diet may lead to defective ossification; but it is of special interest, in view of the obscurity as to causation of the disease, that the structural changes characteristic of rickets in young animals, as well as osteoporosis, may be induced apparently by the simple deprivation of calcium or phosphorus.

The writer (6), from considerations of the metabolism of the two elements in normal and rachitic infants, concluded that the possibility of defective absorption of calcium from the intestinal tract could not be disregarded as a cause of the diminished retentions of both calcium and phosphorus found in infantile rickets, and suggested that the bone softening characteristic of the disease may be secondary to some alteration of the gastro-intestinal conditions which interfered with the normal absorption of an adequate supply of calcium, resulting in a deficient fixation of both calcium and phosphorus in the skeleton. It had also been shown from observations on infants, and, in conjunction with D. Noël Paton, from the results of metabolic experiments on dogs, that the fixation of phosphorus was dependent on a simultaneous fixation of calcium. The two elements indeed are so closely interdependent, both with regard to their excretion and utilization, that a study of one entails equal consideration of the other, a fact ignored by some of the previous investigators.

It is evident then that the factors which modify the absorption of calcium from the intestine are pre-eminently worthy of attention in investigations of the fate of the two bone-forming elements, and especially in the study of ossification.

The present contribution contains the results of further experiments on animals designed to throw light on the process of absorption of calcium and phosphorus.

Description of Method.

Essentially, the method of experiment depended on the fact that nearly all the calcium and the greater part of the phosphorus retained are utilized in skeletal growth. A quantitative examination of the mineral matter of the bones therefore affords an index of the degree of retention and fixation of both calcium and phosphorus over a given period. An estimate of the absorption of the two elements was also obtained by metabolic studies, and from the distribution of calcium and phosphorus in the urine and faeces. In the first series of experiments made in conjunction with D. Noël Paton, dogs were used. A similar series of observations were made on rats in collaboration with Miss P. Henderson.

Young puppies from the same litter were fed on diets identical in every respect except that of calcium content, the variations in the latter being made by the addition of calcium lactate. Towards the end of the growing period the animals were killed and the skeletons examined. The limb bones were carefully cleared of all soft tissue, split longitudinally, and a macroscopic inspection made of the epiphyseal cartilages, marrow, and shaft thicknesses. The specimens were soaked in a mixture of ether and alcohol for several weeks and then dried in a water oven and weighed. In all cases the femur was weighed separately and the amount of mineral matter this bone contained determined by ashing. The ash was finally ground and a sample taken for the estimation of lime and phosphoric acid.

During the course of each period of experimental feeding metabolic studies were made to determine the retentions of lime and phosphoric acid. The urine and faeces collected separately for this purpose were subjected to the usual quantitative examination, special attention being paid to the distribution of the mineral elements. In the experiments on rats the animals were placed in pairs in metabolic cages designed by Miss Henderson. The experimental feeding was begun directly after weaning and was continued till the animals were nearly full grown.

The data obtained from these experiments form the basis of the subsequent discussion.

EXPERIMENT 1

TABLE I

(a) Retention of CaO in Dogs. 3 days' duration.

Animal.	Diet.	Body Weight (gram.).	Intake (gram.).		Weight of Faeces, dry (gram.).	Output (gram.).		Retention per kilo per day (gram.).	
			CaO.	P ₂ O ₅ .		CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .
Ca-poor diet Nos. 1 and 4	Bread 75 gram. Lean meat 60 gram. Butter 4 gram.	3950	0.492	—	23.1	0.039	—	0.015	—
Ca-rich diet Nos. 2 and 3	As above plus calcium lactate 3.3 gram.	3625	4.212	—	27.4	0.348	—	0.16	—

(b) Retention of CaO and P₂O₅ in Dogs. 3 days' duration.

Ca-poor diet Nos. 1 and 4	Bread 160 gram. Lean meat 40 gram. Butter 4 gram.	4385	0.552	3.486	23.3	0.127	3.342	0.016	0.005
Ca-rich diet Nos. 2 and 3	As above plus 6.6 gram. calcium lactate	4435	4.275	3.486	32.2	0.875	1.183	0.127	0.086

TABLE II

Distribution of CaO and P₂O₅ in Excreta. 3 days.

Animal.	Urine.				Faeces.			
	CaO.		P ₂ O ₅ .		CaO.		P ₂ O ₅ .	
	gram.	% of Total.	gram.	% of Total.	gram.	% of Total.	gram.	% of Total.
Ca-poor diet Nos. 1 and 4	0.052	40.9	3.08	92.1	0.075	59.1	0.262	7.9
Ca-rich diet Nos. 2 and 3	0.158	18.0	0.524	44.3	0.717	82.0	0.659	55.7

TABLE III

Comparison of Mineral Matter in Dry Bones (gram.).

Animal.	Body Weight.	Long Bones. Humeri and Femora.	Femora (4).	Ash of Femora (per cent.).	CaO Femora.	P ₂ O ₅ Femora.	Calculated Weight of Skeleton.
Ca-poor diet Nos. 1 and 4	9000	76.6	39.8	40.6	8.91	6.36	99.5
Ca-rich diet Nos. 2 and 3	9070	92.2	47.3	44.3	11.42	8.15	118.2

EXPERIMENT 2

TABLE I

Retention of CaO and P₂O₅ in Dogs. 4 days.

Animal.	Diet per day.	Body Weight (gram.).	Intake (gram.).		Weight of Faeces, dry, (gram.).	Output (gram.).		Retention per kilo per day.	
			CaO.	P ₂ O ₅ .		CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .
Ca-poor diet No. 4	210 gram. bread 155 gram. meat	6270	0.68	5.56	22.4	0.11	3.556	0.02	0.07
Ca-rich diet No. 3	As above plus 4 gram. calcium lactate	5900	3.556	5.56	33.2	0.236	1.413	0.14	0.17

TABLE II

Distribution of CaO and P₂O₅ in Excreta. 4 days.

Animal.	Urine.				Faeces.			
	CaO.		P ₂ O ₅ .		CaO.		P ₂ O ₅ .	
	gram.	%.	gram.	%.	gram.	%.	gram.	%.
Ca-poor diet No. 4	0.055	49.6	3.248	91.3	0.056	50.4	0.308	8.7
Ca-rich diet No. 3	0.07	29.7	0.924	65.3	0.166	70.3	0.489	34.7

TABLE III

Comparison of Mineral Matter in Bones (gram.).

Animal.	Body Weight.	Long Bones.	Femur.	Ash of Femur (%).	CaO in Femur.	P ₂ O ₅ in Femur.	Calculated Weight of Skeleton.
Ca-poor diet No. 2	5900	35.9	10.673	28.2	1.59	1.26	106.7
No. 4	8450	42.7	10.122	26.3	1.34	1.10	101.2
Ca-rich diet No. 1	6000	41.5	11.263	42.1	2.55	1.97	112.6
No. 3	8600	55.6	15.583	36.9	2.958	2.333	155.8

EXPERIMENT 3

Distribution of CaO and P₂O₅ in Excreta of Rats. 4 days.

Animal.	Urine.				Faeces.			
	CaO.		P ₂ O ₅ .		CaO.		P ₂ O ₅ .	
	gram.	%.	gram.	%.	gram.	%.	gram.	%.
Ca-poor P-poor diet Nos. 1 and 2	trace	—	0.028	56	0.024	100	0.022	44
Ca-rich P-poor Nos. 3 and 4	0.04	10	trace	—	0.329	90	0.05	100
Ca-poor P-rich Nos. 5 and 6	0.005	6	0.537	90	0.08	94	0.06	10
Ca-rich P-rich Nos. 7 and 8	0.025	4	0.2	47	0.574	96	0.223	53

EXPERIMENT 4

Distribution of CaO and P₂O₅ in Excreta of Rats. 5 days.

Animal and Diet.	Intake (gram.).		Urine (gram.).		Faeces (gram.).	
	CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .
Nos. 1 and 2 Basal diet of wheat, maize, gelatin, and salt	0.43	0.74	0.008	0.11	0.117	0.149
Nos. 3 and 4 Basal diet plus 0.75 gram. CaCO ₃ -daily	2.79	0.63	0.06	0.02	0.69	0.266
Nos. 5 and 6 Basal diet plus 0.75 gram. CaCO ₃ plus cod-liver oil	3.47	0.78	0.25	0.006	0.66	0.261
Nos. 7 and 8 Basal diet plus cod-liver oil	0.39	0.67	0.01	0.06	0.04	0.065

EXPERIMENT 5

Distribution of CaO and P₂O₅ in Excreta of Rats. 6 days.

Animal and Diet.	Intake (gram.).		Urine (gram.).		Faeces (gram.).	
	CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .	CaO.	P ₂ O ₅ .
Nos. 1 and 2 Basal diet of wheat, maize, and gelatin, Ca-poor	0.58	1.01	0.01	0.275	0.1	0.17
Nos. 3 and 4 Basal diet plus 0.4 CaO as CaCO ₃ added daily	3.72	0.91	0.416	0.006	3.37	0.61
Nos. 5 and 6 Basal diet plus 0.46 gram. CaO as calcium lactate daily	2.09	0.48	0.222	0.005	1.58	0.35

Results.

1. *Experiments on dogs. Experiment 1.* The results recorded in Table I (a) and (b) show that the dogs receiving the addition of the calcium salt (Nos. 2 and 3) retained from seven to ten times more lime than those on the calcium-poor diet, during the period of the metabolic experiment. At the same time there was a corresponding increase in the retention of phosphoric acid with the lime.

The influence of the excess of calcium in the diet on the excretion of the two elements is seen in the results in Table II. With the large intake of calcium there was an increased excretion of this element in the urine, indicating an increased absorption. The greater part of the excess taken was eliminated in the faeces. In the dogs on the Ca-poor diet (Nos. 1 and 4) nearly all the phosphorus excreted was found in the urine. The excretion of phosphorus in the case of the dogs on the Ca-rich diet was strikingly different; more than half of the total phosphorus was eliminated by the bowel.

A comparison of the mineral matter in the bones of the two pairs of animals (Table III) shows that the addition of the calcium salt to the diet had led to an increased skeletal growth. The limb bones of the dogs Nos. 2 and 3 were thicker and stronger than those of Nos. 1 and 4, and, as indicated in the table, much heavier from an increased percentage of mineral matter. The approximate weight of the skeleton was calculated for purposes of comparison from the weight of the femur, the latter being taken as 10 per cent. of the total.

On macroscopic examination of the split bones it was seen that the specimens from the animals on the Ca-poor diet had slightly wider epiphyseal lines and less compact bone in the shafts. No pathological features other than a moderate degree of osteoporosis could be assigned to the specimens Nos. 1 and 4. It will be observed (Table I) that the diet of this pair of animals was rich in phosphorus though poor in calcium, and that the addition of the calcium salt did not upset but rather readjusted the balance of the two elements.

Experiment 2. This experiment was conducted in a manner almost identical with the last. The results were similar. Table I shows that increased

retentions of both lime and phosphoric acid had occurred in the dog (No. 3) fed on the diet to which calcium lactate had been added. The effect of the excess of calcium on the excretion of the two elements was less pronounced, but still clearly indicated in Table II. There was an increased excretion of calcium by the urine, but the excess of calcium above requirements had been eliminated chiefly in the faeces. The fall in urinary phosphorus and the increased output in the faeces were also evident. The effects on the skeleton of the addition of the calcium salt to the diet are strikingly shown in Table III. The bones of the dogs (Nos. 1 and 3) on the calcium-rich diet were thicker, heavier, and stronger, and contained a much higher proportion of mineral matter. The specimens from the animals on the Ca-poor diet (Nos. 2 and 4) could be easily bent and twisted. The lower epiphyses of the radius and ulna were greatly enlarged, and in addition to a thinning of the compact bone of the shaft, there were pronounced rickets-like changes in the limb bones of both dogs.

2. *Experiments on rats.* In these, the growth curves showed that uniform increase in body-weight of all the animals had occurred, and no pathological signs were observed during the course of the observations. Balance experiments were not conducted. The distribution of the mineral elements in the urine and faeces only was determined.

Experiment 3. The chief features regarding the effects on excretion of an excess of calcium in the diet were very pronounced in this experiment. On the phosphorus-poor diet, without the added calcium salt (Nos. 1 and 2), only traces of lime were found in the urine and the phosphoric acid was eliminated in almost equal amounts by the urine and faeces. The addition of the calcium salt resulted in an increased urinary output of calcium (Nos. 3 and 4), while the urine was rendered phosphorus free. The excess of calcium and phosphorus was excreted in the faeces. On the phosphorus-rich diet also the addition of the calcium salt reduced the urinary output of phosphorus very considerably (Nos. 7 and 8). The large increase in both lime and phosphoric acid in the faeces is again evident.

Experiment 4. The basal diet contained moderate amounts of calcium and phosphorus. The results obtained corroborate those of Experiment 3. There was a large increase of urinary calcium when the calcium salt was added to the diet, especially in animals 5 and 6, indicating a greatly increased absorption. As before, the output of urinary phosphorus was markedly diminished, while the faeces phosphorus was greatly increased.

Experiment 5. The excess of calcium was added as carbonate and as lactate. The same effects on the distribution of the mineral elements in the excreta were observed, and necessitate no further comment. A very large increase in the output of calcium by the urine followed the administration of each calcium salt. In both animals the urine was rendered nearly phosphorus free. The increased elimination of phosphorus with the excess of calcium by the bowel was very pronounced.

Discussion.

The chief conclusion to be drawn from these experiments is that the retention of the two bone-forming elements in young animals, and consequently skeletal development, can be influenced by the amounts of calcium and phosphorus in the diet. During the period of active growth the requirement of bone salts is highest, and the results obtained were naturally to be expected. So far, they merely corroborate the work of many previous observers, to which reference has been made.

In the experiments on dogs in which the calcium intake was low, though the diet was rich in phosphorus, skeletal growth was defective and characterized by a deficiency of mineral matter in the bones. Osteoporosis resulted in one pair of animals, and pronounced rickets-like changes supervened in the other pair. The simple addition of calcium lactate to the diet and the consequent readjustment of the balance between lime and phosphoric acid apparently obviated these changes, since the skeleton developed normally. The increased ingestion of calcium had therefore resulted in an increased fixation, not only of lime but of phosphoric acid in the bones, the lime-phosphoric acid ratio of the bone ash of both series of specimens being almost identical.

The influence of the added calcium on excretion was evident in all the experiments. There was a rise in urinary calcium, but the greater part of the excess above requirements was eliminated in the faeces. The urinary phosphorus was considerably reduced and the faecal phosphorus increased. In the experiments on rats in which the intake of phosphorus, as well as calcium, was initially low (Experiment 3), the addition of the excess of calcium rendered the urine phosphorus free.

These results confirm the previous findings of the writer on the effects of an excess of calcium in the diet on excretion in infants, recorded in this Journal (7). They also indicate that, up to a certain maximum, the amount of calcium ingested is an extremely important factor in determining the degree of absorption of this element in growing animals and consequently the utilization of both calcium and phosphorus in bone growth. On the calcium-poor diet the deposition of lime and phosphoric acid was defective, and the metabolic experiments showed that the retentions of these were abnormally low. A consideration of the distribution of the two elements in the excreta makes clear, however, that only a part of the total amount of mineral matter of the diet had been utilized. Calcium appeared in both urine and faeces, while a large part of the phosphorus ingested was absorbed and excreted in the urine. The addition of calcium to the diet was obviously followed by an increased utilization of the element, as evidenced by the increase in retention values and the greater deposition of bone salts. The amount of phosphoric acid excreted by the urine was greatly diminished, and, although the faeces phosphorus was increased, there was a coincident increased fixation of this element in the skeleton by the calcium.

The explanation of these results would seem to be that the *absorption* of

calcium was defective in the dogs on the calcium-poor diet, and that an increase in the intake had led to an increased absorption. The failure in absorption of an adequate amount of calcium from the smaller quantity ingested appeared to have been remedied by the addition of calcium alone, as the diets were otherwise identical. The absorption of phosphorus, as indicated by the output in the urine, was much in excess of requirements on the calcium-poor diet. Fixation, in combination with calcium, was evidently reduced owing to the low absorption of the latter, and defective skeletal growth ensued.

If this explanation be accepted, some important considerations immediately arise regarding the normal process of absorption of calcium. This element, together with phosphorus, is present in food-stuffs, chiefly in insoluble form, the phosphorus generally being in excess. After mixture with the acid gastric juice and the onset of peptic digestion a large proportion of both elements is rendered soluble. The rôle which the free acid of the stomach plays in this process is probably of great importance. The results of the following digestion experiments on milk may serve as a simple illustration of this function.

100 c.c. fresh cow's milk were mixed in an Erlenmeyer flask with 50 c.c. $\frac{N}{10}$ HCl and 25 c.c. of 1 per cent. solution of pepsin. Control tests were carried out by omitting the acid and the pepsin in two separate experiments.

The flasks were placed in an incubator at 37° C. for several hours. The contents were then filtered off and the soluble CaO and P_2O_5 estimated in aliquot portions of the clear filtrates, and calculated to per cent. of original volume.

	Digest.	CaO %.	P_2O_5 %.
No. 1	100 c.c. milk		
	50 c.c. $\frac{N}{10}$ HCl	0.17	0.20
	25 c.c. 1 % pepsin	0.19	0.23
	" "	0.18	0.20
No. 2	100 c.c. milk		
	50 c.c. $\frac{N}{10}$ HCl	0.16	0.175
	25 c.c. water		
No. 3	100 c.c. milk		
	50 c.c. water	0.08	0.10
	25 c.c. 1 % pepsin		

These results show that almost the whole of the calcium and the greater part of the phosphorus were rendered soluble mainly by the acid at comparatively low concentration, and it may reasonably be supposed that a similar action occurs after ingestion in the living subject. In order to test this, the amount of lime in solution in the gastric contents of a dog was determined in the following manner:

A diet consisting of dried milk and meat, to which 8 grm. carbonate of lime had been added, was given for several days to a large hound, weighing 13 kilos.

Three hours after the last meal the animal was anaesthetized and the abdomen opened. The operation was conducted by D. Noël Paton. The stomach, duodenum, and the upper and lower parts of the small intestine were ligatured in sections and removed for chemical examination of their contents. The gastric contents were strongly acid in spite of the large amount of calcium carbonate ingested. The total calcium present was found to be 0.127 gm. CaO per 100 c.c. A part of the contents was filtered. The clear filtrate contained 0.125 gm. CaO per 100 c.c., a result which showed that practically all the ingested calcium was in soluble form in the stomach. The duodenal contents were faintly acid to litmus; the reaction throughout the jejunum and ileum was distinctly alkaline.

Since the reaction of the intestinal secretions is normally alkaline the calcium salts and phosphate held in solution must inevitably tend to undergo precipitation as phosphate of lime, when the acid chyme passes into the duodenum and neutralization begins. That this precipitation does occur would seem to be supported by the facts concerning the mode of excretion of calcium by the bowel. In a previous study on the excretion of calcium and phosphorus in infants on a milk diet (7) it was shown that both the calcium phosphate and the calcium soaps which appear in the faeces are chiefly insoluble residues of ingested mineral matter, and are to be regarded as the forms in which the excess of calcium and phosphorus is eliminated by the intestine. Whether phosphate or soaps predominate in the faeces appears to depend chiefly on the condition of the intestinal contents with regard to free fatty acids. If the latter are in excess almost all the calcium is excreted as soaps. When the conditions tend towards alkalinity, calcium as phosphate preponderates in the faeces. If both fats and phosphate are withheld from the diet, a large part of the excess of calcium is eliminated as carbonate.

It would appear that the conditions of the small intestine preclude the possibility of calcium remaining in solution, and therefore in readily absorbable form after neutralization of the acid chyme has been initiated prior to the onset of tryptic digestion. This would seem to imply that the reaction of the intestine is a very important factor in governing calcium absorption, and that absorption is greatest in the upper part of the intestinal tract. In the light of this hypothesis, it may be of interest to examine the results of previous studies.

In the experiments on dogs, a deficiency in the calcium intake resulted in a defective deposition of mineral matter in the skeleton, apparently from insufficient absorption. Since the faeces contained an appreciable amount of lime it is evident that, in spite of the need for calcium, the dogs on the calcium-poor diet utilized only a part of the amount ingested. On the calcium-rich diet the absorption of calcium was increased, as the evidence of increased utilization showed, but a large part of the ingested calcium was excreted in the faeces. Again, in normal infants on a diet of cow's milk, the retention of lime and phosphoric acid was often less than one-third of the total amounts of these ingested (6). The retention of lime could not be raised appreciably by increasing the calcium content of the diet above a certain limit; the excess of calcium was eliminated by

the bowel. These facts suggest that normally a large part of the intake of calcium remains unabsorbed.

It has also been shown by many observers (1) that in acid feeding or in acid production in the body the urinary calcium and phosphorus are both increased. In 1880 Schetlig found that the ingestion of hydrochloric acid increased the urinary output of the two elements, and similar observations were made by Rüdel. On the other hand, Gehardt and Schlesinger (1899) observed that the administration of sodium bicarbonate had the opposite effect, the urinary calcium being reduced and the faeces calcium increased.

The effects of an excess of calcium in the diet are also in harmony with the view expressed that combination normally occurs in the intestine between the lime and phosphoric acid and tends to limit their absorption. The restriction of an increased quantity of phosphorus to the intestine, with the consequent fall in urinary phosphorus, was evident in all the experiments recorded, and in those in which the diet was poor in phosphorus the addition of calcium salt rendered the urine nearly phosphorus free. Similar results were obtained in the earlier studies on infants (7).

It is of interest to note that Seeman, in 1879, considered rickets to be caused by a deficient absorption of lime, associated with a subnormal content of hydrochloric acid in the gastric juice. A little later, Zander expressed the same idea. Zweifel thought that a deficiency of the hydrochloric acid of the gastric juice interfered with the solution of calcium salts, and attributed rickets to the lack of common salt in the diet. Recently, Zucker, Johnson, and Barnett (8) have drawn attention to the acid-base ion ratio of the diet in the production of rickets in rats. They consider that the reduction of acidity in the intestinal tract may give rise to a significant lessening of absorption of calcium and phosphorus. A diet on which rats could be reared without skeletal defects was converted into a rickets-producing one by the addition of 2 per cent. sodium carbonate.

If the absorption of calcium is chiefly limited to the upper part of the intestinal tract while still in acid-soluble form, it is evident that absorption must be largely influenced by the reaction of the intestinal contents. After solution of its salts has been effected by the acid of the gastric juice, absorption will proceed until the acid mixture of lime and phosphoric acid is rendered alkaline by the intestinal secretions, when calcium phosphate will be precipitated in insoluble form. It can readily be demonstrated by simple experiments *in vitro* that this precipitation from an acid solution begins to occur as soon as the point of neutrality is passed. Since the phosphorus of most diets is in excess of the calcium, the conversion of all the calcium which escapes absorption into phosphate of lime would appear to be almost inevitable. It has been shown (9) that in the presence of an excess of free fatty acids in the intestine most of the calcium is excreted as insoluble soaps, and in the faeces of normal infants on a milk diet a considerable proportion of the total calcium eliminated by the bowel may exist in this form. The formation of insoluble soaps can occur only after the onset of tryptic digestion, and therefore beyond the acid area of the

upper part of the intestinal tract. Whether calcium phosphate or soaps are formed, these combinations can be effected only in the absence of hydrochloric acid. It is noteworthy, however, that phosphate of lime is readily soluble in the lower fatty acids, and in consequence a solution of part of the initially precipitated calcium may occur even during tryptic digestion (9). The possibility of absorption of calcium in this form is of interest in relation to the influence of fat in the diet on calcium utilization. In the case of a persistent excess of free fatty acids in the intestine, as in biliary atresia, the lime in the faeces is almost wholly combined with fatty acids. The ratio of urinary to faecal phosphorus and consequently the absorption of phosphorus are then at a maximum (6). On a diet poor in phosphorus and rich in calcium, the restriction of a large part of the phosphorus to the intestine in insoluble form must conduce to defective absorption of this element. Under such conditions, the presence of free fatty acids in excess in the intestine would facilitate absorption, by promoting the formation of calcium soaps and the liberation of phosphoric acid from insoluble combination. From these considerations it would seem that the absorption of both calcium and phosphorus may be influenced in a significant manner by the reaction of the intestinal contents, and particularly by the concentration of free fatty acids in the intestine.

In the preceding argument it has been assumed that the calcium combinations occurring in the faeces are chiefly unabsorbed residues of ingested calcium formed in the intestine. It has long been held, however, that calcium may be absorbed in excess of requirements and subsequently re-excreted into the bowel. Consequently the calcium which appears in the faeces cannot be regarded as consisting entirely of ingested calcium which has escaped absorption. The intestinal secretions contain minute quantities of calcium and phosphorus, and it has been shown by many workers that calcium passes out by the intestine when its salts are injected subcutaneously or intravenously (10). Recently Salvesen (11) working on parathyroidectomized dogs found that more than nine-tenths of the calcium injected as chloride into the blood-stream were excreted in the faeces. These results demonstrate that the excretion into the intestine of an excess of calcium circulating in the blood does occur. On the other hand, there is no definite evidence that calcium is normally absorbed greatly in excess of requirements from the intestine into the blood. If this took place one would expect that an animal maintained on an insufficient calcium intake would pass practically no calcium in the faeces. As a considerable proportion of the ingested calcium is eliminated by the bowel in these cases, it is reasonable to conclude that, in spite of the urgent demand for calcium by the growing tissues, the intestinal conditions obviate any compensatory increased absorption to supply this need. It is not improbable that the excretion of calcium into the gut is determined by its relative concentration in available form in the intestine and in the blood. The intravenous or subcutaneous injection of calcium salts raises this concentration considerably above the threshold, whereas the blood calcium in healthy subjects remains practically constant, even after the ingestion of large doses of calcium salts.

On these grounds, it has been inferred that most of the calcium combinations which appear in the faeces are derived from ingested calcium salts which have been formed in, and restricted to, the intestine. Whether this supposition be warranted or not, the view is justifiable that calcium absorption is largely limited to the acid area of the intestine, and in considerable part the ingested calcium undergoes transformation into insoluble forms which interfere with its free absorption. If this view be accepted it would appear that the absorption of calcium is normally somewhat restricted. An adequate amount of gastric acid is necessary to ensure the solution of mineral matter in the diet and to retard the precipitation of insoluble calcium salts until absorption in the upper part of the intestinal tract is complete. This function of the hydrochloric acid of the stomach would seem to be of great importance in the assimilation of calcium. The determination of the reaction of the intestinal contents so far made on animals suggests that the acid area over which free absorption may take place is comparatively small, but further experimental work, especially in relation to fat ingestion, is necessary. The integrity of the absorbing surface over this area is in consequence an indispensable factor in normal absorption. For the same reason a considerable excess of calcium over requirements in the intake is necessitated, since a large proportion of the ingested calcium is rendered unabsorbable by the alkaline reaction of the intestinal secretions. It might, therefore, be concluded that defective absorption of calcium would be caused by achlorhydria, or a subnormal content of hydrochloric acid in the gastric juice, by insufficient ingestion of calcium, or by some pathological condition of the upper part of the small intestine lessening the absorptive capacity of its surface. On the other hand, absorption would be facilitated by conditions which tended to maintain the acid reaction of the intestinal contents. The particular type of bacterial activity which predominates in the intestine may be of importance in modifying this reaction.

The absorption of phosphorus takes place mainly in inorganic form, though evidence exists that organic combinations may pass through the intestinal wall (1). In the acid area of the upper part of the intestinal tract, the ingested inorganic salts are associated with calcium and the acid of the gastric juice ensures their solution. Though the loss of part of the ingested phosphorus occurs by its combination with calcium as phosphate when neutralization of the acid chyme takes place, absorption is not restricted in the same manner as that of calcium, since subsequent cleavage of organic phosphorus compounds and the splitting off of phosphoric acid during digestion render a further supply of inorganic phosphate available for absorption (1). Moreover, the total phosphorus of most diets is much in excess of the calcium present. Human milk is a notable exception in this respect, and in relation to the effects of calcium on phosphorus excretion it is noteworthy that the urine of a healthy breast-fed baby is normally phosphorus free. Absorption can be restricted by the addition of an excess of calcium to the diet, but there would appear to be little danger of absorption being seriously diminished apart from this unbalanced condition. It

is of interest to note that some American observers have produced rickets in rats on diets which were low in phosphorus, but contained an excess of added calcium. Zucker and Barnett (12) found rickets in rats after four weeks on a diet of flour and a salt mixture containing 2.9 per cent. of calcium lactate. The addition of either cotton-seed oil or a hydrogenated product of this oil did not prevent rickets. When they lowered the calcium lactate to 1.5 per cent., rickets was still produced. The addition of 20 per cent. of the hydrogenated fat to the diet containing the smaller amount of calcium entirely prevented the onset of rachitic changes. Their interpretation of the result is that '... more insoluble soaps are formed in the intestine, and by precipitating calcium soaps, phosphate in soluble form is made available for absorption'.

The influence of an excess of calcium in a diet relatively poor in phosphorus in restricting part of the latter to the intestine gives considerable support to their explanation, and the action of a persistent excess of free fatty acids in the gut, in altering the normal distribution of phosphorus and calcium in the urine and faeces, previously discussed, renders it still more feasible. Even in such pathological states in infants as biliary atresia, jaundice, marasmus, and fat dyspepsia, an excess of phosphorus is absorbed and excreted in the urine (7). Phosphorus absorption is also facilitated by any condition which maintains the acidity of the intestinal contents or which prevents or lessens its combination with calcium, such as the formation of calcium soaps. When an adequate supply of phosphorus is present in a diet in which the calcium content is not excessive, defective absorption would hardly seem possible; and the chief cause of failure of fixation of this element in the skeleton is defective calcium assimilation as illustrated by the foregoing experiments.

Summary.

1. In growing dogs, osteoporosis and rickets-like changes in the bones were produced on a diet containing a deficiency of calcium but an adequate amount of phosphorus.

2. On addition of calcium lactate alone to this diet, with consequent readjustment of the mineral balance, the skeleton of the dogs developed normally.

3. A study of the excretion of the mineral elements in growing dogs and rats confirmed the results of earlier experiments on the effects of an excess of calcium in the diet on phosphorus excretion.

4. The factors concerned in the normal absorption of calcium and phosphorus are discussed. From considerations of the distribution of the two elements in the excreta, and the data obtained from metabolic experiments, the following conclusions have been drawn:

- (a) The absorption of calcium is initially dependent on the free acid of the gastric juice, which plays an important part in effecting the solution of calcium salts of the diet.

- (b) Absorption is normally restricted by the alkaline reaction of the

intestinal secretions which tend to neutralize and so cause precipitation of the lime in solution as insoluble phosphate.

(c) The free absorption of calcium may be limited chiefly to a comparatively small portion of the upper part of the intestinal tract while still in acid solution. To ensure adequate absorption an excess of calcium in the diet considerably greater than requirements is necessary.

(d) The absorption of phosphorus occurs freely even under pathological conditions, and is difficult to restrict except by the addition of a large excess of calcium to a diet relatively poor in phosphorus.

(e) The fixation of phosphorus in the skeleton is dependent on that of calcium, and in a diet unbalanced with regard to the mineral elements the absorption of an excess of phosphorus is followed by its excretion in the urine.

5. A rôle which the fats in the diet may play in facilitating the absorption of calcium and phosphorus is suggested.

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RENAL GLYCOSURIA: A CLINICAL AND METABOLIC STUDY

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THE term 'renal glycosuria' is applied to a condition in which there is an undue permeability of the kidneys to sugar, the concentration of the sugar in the blood remaining within the normal limits. The quantity of sugar excreted is usually small, being either unaffected or not much increased by carbohydrate food. The patients continue in good health over a period of years, as symptoms of diabetes mellitus do not develop. There is a marked contrast between renal and true diabetes in that in the former the function of mobilization, storage, and utilization of sugar is unimpaired.

Case Reports.

The following cases, six in number, have been observed at the Montreal General Hospital. The clinical features are first given. The combined laboratory data of all cases will be recorded and discussed separately.

Case I. Hospital No. 2148/23. Male, labourer, aged 51, came to the Diabetic Clinic and was admitted to the ward April 24, 1923. He stated that he was treated in this hospital by one of us for diabetes in November 1894, and on referring to the records it was found that he was a patient in the wards from November 1894 to March 1895, with the diagnosis of glycosuria. He complained then of thirst and weakness, obesity and general pains. He stated that he had had abdominal pain, headache, and insomnia for five years, and for two years had been unable to do heavy work on account of weakness. He weighed 189 lb., had a thick adipose layer, and passed 33 oz. of urine in 24 hours with 1.04 per cent. of sugar. Acetone was present. During the winter sugar was present on and off in spite of a restricted diet. When discharged he was sugar free and weighed 178 lb.

On leaving the hospital he was well enough to work as a labourer for three years. After that he never felt strong, having frontal headaches and pains in the sacral region and was obliged to give up heavy work. He had always had a good appetite, the bowels had been regular, and there had been no thirst or polyuria. He had always been a poor sleeper, getting only three or four hours at

night. He used tobacco and alcohol moderately, was unmarried, and had not had any venereal disease. In two brothers sugar had been found in the urine. One was killed accidentally, aged 48, when apparently in good health, and the other brother was healthy.

Present condition. The patient was a healthy-looking, large-framed man, and weighed 175 lb. Height 5 ft. 5½ in. He stated that he was not strong and was unfit for heavy work. The chest was well developed, the heart normal, and the apex 9 cm. from the mid-line. The pulse 72 to 92, B.P. 148-86. The teeth were decayed and there was pyorrhoea. The temperature during his stay in the hospital showed slight elevations to 99° or 99.4° every two or three days, for which no cause, apart from pyorrhoea, was discovered. The lungs and abdomen were normal. The pupils were equal and active to light and the tendon and superficial reflexes were normal.

The urine on admission was acid, S.G. 1.030, no albumin, 0.873 per cent. sugar, and 400 c.c. were passed in 24 hours, containing 3.48 gm. of sugar. No acetone or diacetic acid. R.B.C. 4,770,000. W.B.C. 11,800. Poly. 71 per cent., small mono. 19 per cent., large mono. 8 per cent., eosinophils 1 per cent., basophils 1 per cent. Blood Wassermann negative. Dr. Mathewson reported the retinal arteries of silver wire character, but the fundi were otherwise normal. Blood-sugar findings during the entire period of observation were normal.

This case, first observed 29 years ago, at the age of 22, without developing polyuria, thirst, or emaciation, was of itself sufficient proof of 'renal diabetes', and this diagnosis was fully confirmed by the laboratory findings.

Case II. Hospital No. 790/23. Male aged 51, was admitted for observation, having had sugar in the urine for 10 years. In 1912 he had a haematuria of unknown origin, and on examination sugar was then found in the urine. The patient appeared to be healthy and there were no subjective nor objective signs of diabetes mellitus other than the glycosuria. Restriction of diet had been very irregularly carried out. A son had sugar in the urine.

Case III. Hospital No. 2221/23. Female aged 22. A nurse in training in this hospital. Following her laboratory training in urinalysis in May 1922, she examined her urine and found sugar. There were no other signs of diabetes mellitus. She was in good health and very active on duty. Her mother had sugar in the urine.

Case IV. Hospital No. 624/23. Male aged 42, came to the hospital for observation because he was refused a life insurance policy, sugar having been found in the urine. He was a very active business man, a broker, and there were no other signs, subjective or objective, of diabetes mellitus. The family history was negative.

Case V. A. P. Female aged 32, was admitted for observation because a glycosuria was discovered during the third month of pregnancy. There were no other signs of diabetes mellitus. The physical findings, with the exception of the pregnancy, were entirely negative.

Case VI. Hospital No. 1271/23. Male aged 10. During the course of typhoid fever in 1922, sugar was found in the urine. This in spite of restriction in diet had persisted. The quantity excreted in 24 hours was always less than 10 gm. Acetone bodies were only found during the period in which the diet was restricted. He was a very active boy. The physical findings were negative.

Clinical Features.

Incidence. Allen found three cases of renal glycosuria in 40 diabetics, an incidence which is probably unusually high. In 275 consecutive cases of diabetes observed at the Montreal General Hospital, all fully investigated for carbohydrate tolerance, including blood and urine analyses, six such cases occurred. One of these was sought out as the relative of another patient, so that in this series five, or approximately 2 per cent., applied or were referred to the metabolic clinic as diabetics.

Family history. Several writers refer to the family character of this condition, and although no reference is made to this point in a number of the reported cases, it appears sufficiently frequently to constitute a cardinal feature of this condition. Of the 69 cases collected in the literature 15 gave a family history. Saloman, in the families of two sisters, found three children and a grand-child affected in one, and two out of seven children in the other. The mother of these women had eight brothers and sisters, several of whom had diabetes, one case being of a severe type. Cammidge records a case in father and son. In one of Graham's cases a brother had glycosuria. In another the father had glycosuria, and two others were brother and sister. In our first case two brothers had glycosuria. In Case II father and son were affected, and in Case III the mother was similarly affected.

Sex. Males are much more frequently affected than females. Of the cases collected from the literature and including our own cases, 48 were males and 21 females.

Age. Of the 69 cases, the youngest was a child of 6 years (Labbé). Five were under 10 years of age, 16 between 10 and 20 years, 25 between 20 and 35 years, 15 between 35 and 50, 6 between 50 and 60 years, and only 2 were over 60 years. The greater incidence noted during the third decade of life is probably more apparent than real, the number of insurance applicants being greater at this period of life.

The affection may descend through father or mother, or it may be a family tendency, the parents being sugar free. Apart from hereditary influence a noteworthy aetiological factor occurred in one of Allen's cases, in which a severe shell concussion was followed by glycosuria in an officer previously sugar free. In Labbé's case a mild nephritis following scarlatina was accompanied by renal glycosuria. In pregnancy the glycosuria frequently found appears to be of this type, the blood-sugar being normal. Küstner (1) regards the condition as common in pregnancy, finding it in all of 21 cases between the thirtieth and thirty-third week.

Symptoms. As a general rule the patients are free from symptoms, the glycosuria being discovered in the course of routine examination or in applicants for insurance. They may go on for many years with a mixed diet without developing any sign or symptom of diabetes. Parkes Weber records a case where a woman still had sugar at an examination made thirty years after it was first

discovered, and in our first case sugar was present 29 years after it was first found. Many cases are on record for periods of two or three years up to ten or twelve without other symptoms of diabetes mellitus.

In only a minority is complaint made of any disability. In Saloman's tenth case there was thirst and exhaustion, in another a tendency to palpitation with sexual neurasthenia. Beard and Grave record a case with slight polyuria, Bailey one with a lack of reserve energy, and Murlin and Niles an instance with thirst and polyuria for a period in which the other criteria were fulfilled for renal glycosuria. In our first case there was weakness, sufficient to oblige the man to change his occupation from that of a labourer to lighter employment, and in the early stage of his malady thirst was present. Vulvitis is also mentioned as being present in one instance.

The quantity of sugar excreted daily in a majority of cases is not over 10 gm. in 24 hours, and the concentration $\frac{1}{2}$ per cent. or less. It is but slightly, if at all, influenced by the carbohydrate content of the diet. It is not apt to appear after food when not present before, as in the case of mild diabetes. It is usually constantly present. The urine is at times sugar free and a carbohydrate meal is then not apt to cause glycosuria, as is always the case in diabetes mellitus. The lack of response to a carbohydrate diet is well illustrated by a case of de Langen's when 4 to 19 gm. were excreted daily on a liberal carbohydrate diet (184 to 503 gm.), whilst on a carbohydrate-free diet there were 5.8 to 19 gm. In a case of Saloman's, after the administration of 100 gm. of grape sugar the urinary sugar only rose from 0.108 to 0.124 per cent. Graham calls attention to a class of cases in which the glycosuria is more abundant, 10 to 50 gm. or more daily, which react somewhat differently to the milder form. The blood-sugar rises to a higher point after a carbohydrate diet than in normal individuals, and 7 to 17 per cent. of the ingested sugar is excreted instead of 1 to 2 per cent. These cases, however, run a prolonged course and do not develop into diabetes. Thus two of Graham's cases, in a brother and sister of 12 and 14 years, continued in good health for 4 and 6 years, and the one of Parkes Weber's already referred to was under observation at different periods during 30 years. In this group of cases observed at St. Bartholomew's Hospital, the excretion of glucose when the blood-sugar stood at a normal or subnormal figure indicates that they differ essentially from diabetes. They also present the family incidence so frequently seen in renal diabetes. The presence of acetone and diacetic acid is not infrequent in these cases, but in the majority of instances these bodies are the result of starvation or of a too restricted carbohydrate diet.

Another classification is based upon the presence or absence of albumin and casts, or of defective function of the kidneys. The presence of albumin and casts in Klemperer's first case is responsible for the term 'renal diabetes', and this writer regarded renal changes as an essential part of the syndrome, by rendering the kidney more permeable to sugar. Labbé also, writing in 1922, asserts that renal changes or defective function are always present. This view, if correct, would be a satisfactory explanation of the glycosuria, as it is well recognized

that in certain cases of nephritis, as reported by Naunyn, or in early stages of nephritis produced by cantharides or uranium, glycosuria may appear. As the lesions advance it is generally recognized that the excretion of sugar lessens or disappears from the urine, whilst it increases in the blood. On the other hand, in the glycosuria from phloridzin in experimental work by Fahr, no renal changes could be demonstrated. In Case I of our series, after careful investigation, no evidence of renal insufficiency was found. It may therefore be stated that defects in renal function form no necessary part of the malady. In many of the cases reported, the similarity of phloridzin glycosuria is mentioned. More recent work on this subject (2) points to the view that phloridzin not only affects the permeability of the kidney tissue to blood-sugar, but produces an impairment in the sugar-burning mechanism. Renal diabetes is not regarded as being associated with such a disturbance in the sugar-burning mechanism.

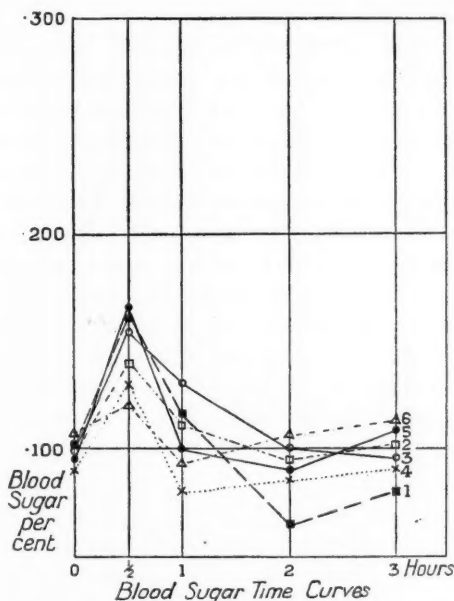
Laboratory Data.

The observations made in our cases consisted of the following: (a) Blood-sugar time curves following the ingestion of glucose; (b) effect of diet on the excretion of water, acid bodies, and carbohydrates; (c) blood-sugar analysis daily before meals or after meals at different intervals; (d) renal efficiency tests; (e) gaseous metabolism studies concerning the storage and rate of utilization of glucose following ingestion; and (f) studies of glycuressis, including observations on the excretion of fermentable, non-fermentable, and hydrolysable reducing substances in the urine.

Blood-sugar time curves. Each patient during the post-absorptive state, 15 hours after the evening meal, received 1.75 gm. of glucose per kilo body-weight (3) dissolved in 250 c.c. water flavoured with lemon juice. Blood and urine sugar estimations were made before administration of the glucose, and then 30, 60, 120, and 180 minutes after. For brevity, the results are graphically recorded in the chart on p. 265. It will be noted that in all cases the curves were of the accepted 'normal' nature. The blood-sugars before administration of the glucose were normal. In no case was the generally accepted threshold reached (0.160-0.180 per cent.), and all blood-sugars returned to their original levels in less than 2½ hours.

Since the other data in all the cases agreed in essentials, for brevity, with the exception of the studies on glycuressis, only those of Case I are here recorded. This case was chosen particularly because it conforms to the most important clinical sign which establishes the diagnosis—the patient must not subsequently develop symptoms of diabetes mellitus. The importance of this sign cannot be too strongly emphasized. As Joslin points out, 'it is clinically dangerous to make a diagnosis of renal diabetes until the patient has been under observation for several years'. This patient, as recorded above, has had glycosuria for twenty-nine years.

Renal function. The complete data of all renal efficiency tests are recorded in Table I. The renal test-meal shows a normal salt, water, and nitrogen balance, and a normal variation in volume and density in the periodic (two hour) specimens. The night urine is normal in volume and concentration of salt and nitrogen. The concentration of urea in the urine following ingestion of 15 gm. urea is normal (4). The urea concentration factor is normal (5). The values of the non-protein nitrogenous substances and chlorides of the blood are within the normal limits. These data are therefore in accordance with the view stated above that defects in renal function form no necessary part of the affection.



Effect of diet. The data obtained on the effect of diet upon the blood-sugar and the excretion of water, sugar, acid bodies, and ammonia are recorded in Table II. The patients, while under these observations, were under the accepted standard conditions for accurate metabolism studies. All foods and fluids were carefully prepared in the metabolic diet kitchen, and their food value, including the water-content of the solid food, computed from the Atwater-Bryant Food Tables (6). The carbohydrate content of the diet was gradually increased from 193 to 465 gm. Calculated on the Woodyatt basis (7) the total available glucose from all sources, carbohydrates, fats, and proteins, was increased from 251 to 527 gm. It will be noted that at no time was there any relation between the amount of carbohydrates ingested and excreted. The maximum amount excreted during a twenty-four-hour period was 19.8 gm., and less than half of this amount was excreted when the carbohydrate content of the diet reached its maximum. Blood-sugar estimations made before meals, and thirty,

sixty, and ninety minutes after meals, showed persistently normal values. The values for the titratable acid, titratable acid plus ammonia, total organic acids, and ammonia were normal throughout the period of observation, including the day when an excessive amount of fat was given. On one day, when insulin was given before each meal, the total sugar excreted did not differ from the average amount excreted daily during the period of observation. This had been interpreted by Campbell¹ as due to the fact that, though the blood-sugar was normal, it was not lowered to the actual threshold of the patient. If sufficient insulin were given to cause a hypoglycaemia to below the threshold point no sugar would have been excreted. Unfortunately, this suggestion was made after the patient was discharged from the hospital.

Gaseous metabolism. What are probably the most important of all the data obtained are those concerning the study of the sugar-burning mechanism. So far as we could ascertain from the literature, such data are here recorded for the first time in the study of renal diabetes; Garrod (8), in his discussion on non-diabetic glycosurias, indirectly emphasizes the value of such studies. He states that 'no form of glycosuria which has its origin in an impairment of the power of burning glucose, whether or not it be accompanied by an increased mobilization of sugar within the organism, can, on scientific grounds, be excluded from the diabetic category'. Allen (9) notes that the excretion of sugar must be due to abnormal permeability of the kidney while the tissues still retain the normal power of utilizing dextrose, and later (10) suggested that the study of the respiratory metabolism might yield some information concerning the carbohydrate economy in renal glycosuria cases. He states 'such a study should yield information concerning the rate of utilization and storage of glucose'. The average results of such experiments in normal individuals have been obtained (11). The procedure was the same as that followed in the establishment of the normal values. A Tissot gasometer, Haldane gas analysis apparatus, and half-face Siebe-Gorman mask were used. The accepted standard (12) technique was followed. The respiratory quotient and metabolic rate were found before, and 15, 30, 60, 90, 120, 150, and 180 minutes following, the ingestion of 1.75 grm. glucose per kilo body-weight. Urine nitrogen estimations were not made. As pointed out before (11), the uncertainty that the urine nitrogen obtained at the time of the test represents the protein metabolism at the time of the test makes results so obtained of doubtful value. The respiratory quotients are, therefore, not of the non-protein type. This does not materially alter the value of the results, since the 'normal' values were obtained under the same conditions, and comparisons can thus be made. From the respiratory quotient and metabolic rate values the calculations for the utilization of the carbohydrate are made. 15 per cent. of the total calories per hour are deducted for the protein metabolism (13). The remaining calories, assumed to be derived from the carbohydrates and fats, are apportioned according to the Zuntz-Schumberg tables as modified by Williams, Riche, and Lusk (14). The combined results, including the blood-

¹ Personal communication.

sugar time curve obtained at the time of the test, are recorded in Table III. It will be noted that not only was the carbohydrate utilized, but in the case recorded it was so with a greater avidity than the average normal individual. Over 23 per cent. of the total glucose ingestion was oxidized within three hours; the remainder is assumed to have been stored, since only 3.72 grm. were excreted during the period of observation. The blood-sugar time curve obtained during this period, as on a former occasion, was normal. The possibility that the assumption that all the glucose ingested has left the stomach during such a test is incorrect has recently been pointed out by Benedict (15). The introduction of a 40 per cent. solution of glucose into the stomach may be an abnormal phenomenon, and on account of its hypertonic state neither normal absorption nor elimination need be expected. This appeared to be such an important factor in the interpretation of the results, not only in this case but in the study of all blood-sugar time curves, that a short study was made of this problem. Of twenty normal individuals, each of whom received during the post-absorptive state 100 grm. glucose dissolved in 250 c.c. of water (40 per cent. solution), only two showed any evidence of retention (bismuth shadow in the X-ray plates) three hours after the ingestion of the mixture. These results are not in accord with those of Johansson (16), who made similar observations with X-rays. The latter, however, used 200 grm. of glucose. Considering the possible sources of error, such as delayed absorption from the intestines, short periods of observations, &c., the results obtained can be but an approximation of the truth. The findings are, however, significant, differing widely from those obtained even in a very mild diabetic, such as a sugar-free case, and with a tolerance of approximately 250 grm. carbohydrate.

Glycuresis. To interpret the results obtained in this study of these cases recorded concerning the excretion of carbohydrates it appears necessary, at least briefly, to point out the basis of this work. Depending upon qualitative tests for reducing sugars it is generally assumed that the presence of sugar in the urine is not a physiological phenomenon. It is also generally accepted that the excretion of sugar in the urine is a function of the concentration of sugar in the blood. A definite threshold point, a blood-sugar value below which sugar is not excreted, is recognized. Though differing in different individuals, this threshold point lies within narrow limits, 0.160 to 0.180 per cent.

Blood- and urine-sugar studies are by no means new (17); Tiedman (18), in 1831, first observed that sugar was normally present in the urine. In 1848 Claude Bernard showed that sugar was constantly present in the blood of an animal on a carbohydrate-free diet, and again in 1856 Chaveau showed that sugar was a constant constituent of the blood. Claude Bernard (19) described a method for the estimation of sugar in the blood, and the normal value found, 90 mg. per 100 c.c., holds to-day. The correlation of blood and urine is also not new, Bernard, and later Hofmeister (21), having given this consideration. Threshold values have been recorded by numerous observers. Of special note are those of Graham (20), Jacobsen (22), Bing (23), Foster (24), and Hamman and Hirschman (25). Bailey (17), in his review of this subject, records the main facts.

Briefly, the average accepted threshold lies somewhere between 0.160 and 0.17 per cent. The tolerance on an empty stomach is commonly accepted as 150 gm. glucose. But Myers (26) found glycosuria, following the ingestion of 75 gm. glucose, in a normal subject. Goto and Kuno (27) found a glycosuria in twenty-two cases of fifty-three subjects after 100 gm. Of 100 glucose tolerance tests made in this hospital² on patients coming to the Outdoor Department with examinations negative, subjectively and objectively, for diabetes, twenty-two had a glycosuria following the ingestion of 100 gm. glucose. Woodyatt (28), by continuous intravenous injections of glucose, found the tolerance to be 0.85 gm. per kilo per hour. The rate of glucose absorption from the alimentary tract never exceeds 1.8 gm. per kilo per hour. Recently (29) the absolute existence of a threshold point below which sugar does not appear in the urine has been further emphasized by Folin and Berglund. These authors state that 'the absence of any unmistakable glycosuria following the ingestion of 200 gm. glucose is also important in that it proves the concept comprised in the term glucose threshold to be not only something approximately true; the concept is absolutely correct, however uncertain the exact figures given for the threshold may be. Hyperglycaemia below the threshold does not normally produce the slightest leakage of glucose through the kidneys, and normally not a trace of absorbed and circulating glucose is lost.'

This appears to negative the early observations of Baisch (30) and Breul (31) and also those of Pavy (32), who considered that sugar was a constituent of normal urine. In much of the work concerning the excretion of sugar in the urine the quantitative method for its detection, Fehling's or Benedict's solution, was used. Benedict (33) points out the inaccuracies of such methods: though Fehling's solution gives at times no visible reaction with as much as 0.100 per cent. glucose solution in urine, a reaction will be noted in as weak a glucose solution as 0.001 per cent. in water. This phenomenon is explained by the fact that urine contains substances which interfere with the reaction, creatinine and urea. The former directly holds any cuprous oxide formed in solution, and the latter indirectly by being converted into ammonia during the heating process. In a more recent publication Benedict (15) reviews the subject of sugar excretion, especially the work of Folin and Berglund, and concludes that the threshold for sugar excretion is an artefact. Sugar normally is present in the urine, though the total fermentable by yeast constitutes less than half of the total reducing substances. Benedict does not accept the view that the reducing substances normally present are due, as Folin suggests, to the absorption of foreign unusable carbohydrate material present in the food ingested.

Observations along these lines have been made in the hospital in cases of normal individuals, diabetics active and 'sugar free', and in the cases of renal glycosuria. The method employed for the partition of the fermentable, non-fermentable, and hydrolysable portions of the reducing substances in the urine was that described by Benedict.

² A detailed study of these cases is in preparation for publication.

In Table IV are recorded the data of the first six normal, 'sugar-free' diabetics and the six renal glycosuria subjects. The many factors which might influence the excretion of these reducing substances are discussed in detail, both in the reports of Folin and Berglund and Benedict and Osterberg. The interesting observation here, however, is that the average results obtained in the normal subjects approximate closely to those obtained in the diabetics who were 'sugar free'. In the case of the renal glycosurics, not only the fermentable, but also excretion of the non-fermentable and reducing substances, after hydrolysis were increased. The chance of this being due to non-usable carbohydrates in the food in each one of the six cases does not appear probable. If Benedict's conception of the phenomenon of glycosuria is correct, in renal glycosuria the kidneys are more permeable than normal to all forms of carbohydrates.

Because of the different clinical pictures associated with the excretion of sugar the terms renal diabetes, diabetes innocens, and renal glycosuria are met with. Since they all agree in the essential clinical features—the long life and no evidence of a disturbance in the rate of utilization of carbohydrates, and in view of the newer conception of the mechanism of the excretion of sugar—the term renal glycosuria appears to be from a practical clinical point of view more appropriate.

The recognition of these cases is of considerable importance, as it spares the victims from being submitted to a rigid diabetic regimen. In several instances in which it has been tried the patients complained of weakness, and a mild degree of acidosis has been produced which has forced the abandonment of this form of treatment. In this connexion the observations of Frank are worthy of note. The fact that it is at times impossible to render the patient sugar free is not a sign of gravity, but dependent upon the renal nature of the trouble. Graham recommends a restricted carbohydrate diet for some months in the type of case which he found at St. Bartholomew's Hospital, but as his cases appeared to do well for years without any restrictions it seems doubtful whether such a precaution is necessary.

That these cases are of long duration is of importance to insurance companies, and there seems no reason why they should be classified as 'sub-standard' and not be accepted at the ordinary rates.

The writers wish to express their appreciation to Miss Althea Frith for technical assistance.

TABLE I
Renal Function.

Renal test-meal:			Balance.	
Periodic Specimen.				
Hour.	Vol. c.c.	S. G.	Intake.	Excreted.
8-10 a.m.	160	1016	Water -1650	1220
10-12	210	1009	Salt -7.04	6.64
12-2 p.m.	220	1006	Nitrogen 10-14	9.76
2-4	250	1008		
4-6	70	1020		
6-8	60	1022	Night urine 245 c.c. : 1.62 % nitrogen,	
8 p.m.-8 a.m.	245	1030	0.80 % salt.	
			Solids excretion total 39.3 gm. ;	
			day/night ratio 1.48.	

Urine urea concentration test following ingestion of 15 gm. urea :
1st hour, 3.24 % 2nd hour, 3.36 %.

Blood : Urea nitrogen 21 mg. per 100 c.c.
Creatinine 1.36 mg. per 100 c.c.
NaCl 5.004 gm. per litre (plasma).
Urea coefficient = 52.

TABLE II
The Effect of Diet upon the Blood-sugar and Excretion of Water, Sugar, Acid Bodies, and Ammonia.

Date.	Urine.							Blood.	Diet.				Total Available.
	Sugar.			c.c. N/10 Acid Bodies.					COH. gm.	Fat. gm.	Pro. gm.	Water.	
	Vol.	%	gram.	Titrat. Acid.	Tit. Acid + Ammonia.	Total Organic Acid.	NH ₃ gm.						
Apr. 25	400	0.87	3.4	121	337	320	0.36	0.094	193	106	82	850	251
26	1800	0.83	14.9	417	1087	864	1.1	0.100				2500	
27	625	1.33	8.3	400	887	684	0.81	0.093	250	100	75	1050	303
28	1300	1.23	15.9	400	1024	915	1.0	—	320	98	82	1860	377
29	775	2.56	19.8	310	837	806	0.89	0.125	376	94	76	1040	429
	Blood taken 30 min. after meals												
								0.125					
								0.100					
30	1225	0.60	7.3	294	847	748	0.94	0.100	410	98	84	1825	469
	Blood taken 60 min. after meals												
								0.103					
								0.100					
May 1	1350	0.65	8.9	378	918	810	0.91	0.122	465	96	92	2050	527
	Blood taken 90 min. after meals												
								0.098					
								0.111					
2	750	1.42	10.7	405	870	570	0.79	0.120	416	92	86	1090	475
	5 units insulin 30 min. before each meal												
3	900	1.71	15.4	360	799	520	.74	0.135	385	210	78	1460	527

* Post-absorptive blood-sugars unless otherwise stated.

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TABLE III

Utilization, Storage, and Excretion of Glucose following the Ingestion of Glucose (Blood, Urine, and Gaseous Metabolism Studies).

Height 160.5 cm. Weight 78.6 kgm. Body surface 1.83 sq. m. (Du Bois). Dose of glucose 136.5 (1.75 grm. per kgm.).

Gaseous Metabolism.

Period.	Resp. Quot.	Cal. per hour.	Rise Cal. per hour.	In Cal. per sq. m. per hour.	% Cal. from Basal.	Cal. from COH & Fat.*	% Cal. from COH.†	Cal. from COH.	Grm. COH Utilized. Total per hour.	Grm. COH Utilized. Total Utilized.	Blood Sugar mg. %.	Grm. Sugar.
Basal	0.836	73.27	0.00	40.38	—	62.27	42.2	26.26	—	—	0.102	—
15 min.	0.889	75.47	2.20	41.23	2.1	64.14	45.6	29.23	7.12	1.78	0.103	—
30 "	0.880	81.37	8.10	44.46	10.1	69.16	59.2	40.94	9.98	2.49	0.145	0.520
60 "	0.913	80.89	7.62	44.20	9.4	68.75	69.4	47.70	11.60	5.80	0.136	—
90 "	0.886	85.57	12.30	46.75	15.8	72.72	59.2	43.04	10.40	5.20	0.100	1.426
120 "	0.891	79.74	6.47	43.57	7.8	67.77	62.6	42.41	10.3	5.15	0.084	0.836
150 "	0.923	78.18	4.91	42.72	5.7	66.44	72.8	48.35	11.7	5.85	0.097	0.621
180 "	0.900	79.27	6.00	43.31	7.2	67.37	66.0	44.46	10.8	5.40	0.110	0.319
Total										31.67		3.722

* 15 per cent. deducted for protein metabolism (Voit).

† From modified Zuntz and Schumberg tables (Lusk).

Résumé: Total glucose ingested 136.50 grm.

Total glucose excreted 3.72 "

Total intake 132.78

Total utilized 31.67 per cent. of total intake - 23.8

Total stored 101.11

TABLE IV

Glycosuria and Glycuresis in Normal, Diabetic (treated and untreated), and Renal Glycosuria Subjects.

Grams Reducing Substance per 24 hours.

Remarks.

No.	Reducing before Hydrolysis (a).	Reducing after Hydrolysis (b).	After Fermentation (c).	(Non-reducing) Total Hydrolysable (b-c).	Total Fermentable (a-c).	Fermentable % of Total Reducing Subs.	Subject.
1	0.720	0.876	0.436	0.156	0.284	39.5	Normal
2	0.834	1.021	0.596	0.187	0.238	29.6	"
3	1.003	1.162	0.834	0.159	0.169	16.9	"
4	0.724	0.964	0.304	0.240	0.420	58.1	"
5	0.301	0.379	0.208	0.078	0.093	30.9	"
6	1.570	1.875	1.425	0.305	0.145	9.3	"
7	8.28	8.32	0.408	0.040	7.872	—	Diabetic (active)
8	0.473	0.913	0.462	0.440	0.011	3.4	" (sugar free)
9	0.404	0.602	0.370	0.190	0.034	8.5	"
10	0.414	0.657	0.270	0.243	0.144	34.8	"
11	0.260	0.487	0.201	0.227	0.059	22.7	"
12	1.806	2.114	1.638	0.308	0.168	9.4	"
13	8.30	9.62	1.304	1.320	6.996	—	Renal glycosuria
14	15.90	17.78	0.984	1.880	14.916	—	"
15	5.831	7.423	1.629	1.592	4.200	—	"
16	6.426	8.019	1.782	1.593	4.644	—	"
17	8.9	10.6	1.264	1.700	7.636	—	"
18	10.7	12.4	1.516	1.700	9.184	—	"

Average Excretion per 24 hours (grm.).

Polysaccharides Non-reducing.

Non-fermentable Reducing Subs.

Fermentable Reducing Subs.

Normal

0.187

0.633

0.224

Diabetic (sugar free)

0.283

0.588

0.083

Renal glycosuria

1.630

1.413

7.827

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THE ASSOCIATION OF BLUE SCLEROTICS WITH BRITTLE BONES AND PROGRESSIVE DEAFNESS

By WILLIAM STOBIE

With Plate 18

Historical Introduction.

In 1880 Eddowes (1) noted the association of dark blue sclerotics with fragility of the bones in a boy whom he attended for two years with nine separate fractures. Twenty years later, at a meeting of the Dermatological Society of Great Britain and Ireland, he showed a patient—a young woman—suffering from eczema, with such extraordinary transparency of the sclerotics that the dark pigmentation of the choroid was visible through them. On questioning the patient it was found that she had broken several bones from slight injuries and that her father had the same type of eyes, and that he also had on several occasions sustained fractures from trivial causes.

In 1908 Peters (2) gave an account of a family with blue sclerotics, but did not mention fragility of the bones. Five years afterwards, at Conlon's request, he obtained further information about the family, when it was found that there was a marked history of fractures.

In 1910 Stephenson (3) described four generations of 32 individuals, in 21 of whom blue sclerotics were present. In the same year Harman (4) extended this family to five generations of 55 individuals, 31 of whom had this anomaly.

In 1911 Burrows (5) published a pedigree of four generations comprising 29 individuals. Thirteen of these had the apparently pigmented sclera, and in 9 out of the 13 brittle bones occurred as well. In the same year J. D. Rolleston (6) showed a child of 9 months with blue sclerotics and a spontaneous fracture of the humerus to a meeting of the Royal Society of Medicine. The mother of the child, the mother's sister, and grandmother had the same type of eyes, but there was no history of fragilitas ossium among them.

In 1912 Adair-Dighton (7) traced four generations of 14 persons, of whom 9 had blue sclerotics. In five out of this number fractures were also noted. One of the five—a woman—suffered from nerve deafness which commenced at 21 years of age.

In 1913 Adam (8) described the case of a man aged 31 and his brother, both of whom had blue sclera and both of whom had sustained numerous fractures, while

the remaining members of the family were free from these abnormalities. The case of a boy aged 14, similarly affected, was also reported. No other degenerative changes were found.

In the same year Behr (9) published the case of a woman aged 38 with deep blue coloration of the sclera, bulging of the cornea, defective hearing since the age of 19, and numerous dislocations from ordinary movements.

Conlon's (10) group consisted of five generations. Of 27 individuals 18 had blue sclerotics, and several of these had suffered from multiple fractures.

In 1913 also, Poynton (11) showed to the Royal Society of Medicine a child of 11 who had never been able to walk alone and who had darkly coloured sclera with a history of frequent fractures. At a later meeting in the year of the same society, Langmead (12) discussed the case of a boy aged $9\frac{7}{12}$ who had always been backward physically and mentally and who had had two fractures from slight causes. Stephenson, who was in the chair, remarked on the presence of blue sclerotics in the patient and considered the case should be regarded as another example of the syndrome.

In 1914 Cockayne (13) inquired into the family history of a child aged $1\frac{1}{2}$ with blue sclerotics, and who was supposed to be suffering from rickets. Six other members of the family were found to have coloured sclera and a history of multiple fractures and sprains. Ostheimer (14) reported the case of a child 3 years old who had had seven fractures, and who had dark blue sclerotics. No other instances of the combination were found in the rest of the family.

Hofmann (15) in 1915 published three cases of the association of the ocular and osseous abnormalities with a familial history in two of the patients. Hermann's (16) case occurred in a boy of 2 years.

In January 1916 Van der Hoeve and de Kleyn (17) demonstrated to the Groningen Medical Society the association of deafness with the abnormal coloration of the sclerotics and the fragilitas ossium, and their first paper was published in the next year (Fig. 2).

Bronson (18), who began her investigations in December 1915, published in 1917 an exhaustive article with a copious bibliography. She described one family with blue sclerotics and brittle bones consisting of four generations and 55 individuals, of whom 7 commenced to be deaf in early adult life. No member of the family without fragilitas ossium and blue sclerotics suffered from deafness. In another family of three generations and 8 individuals 7 had blue sclerotics, and 4 of these had sustained fractures.

In 1918 Voorhoeve (19), in reporting a family, discussed the association of other abnormalities with the syndrome.

In 1921 Blegvad and Haxthausen (20) described a family consisting of three generations and 23 individuals, of whom 10 had blue sclerotics, 8 had blue sclerotics and had sustained fractures, and in 3 there was deafness superadded. Among the individuals with white sclerotics there were two instances of deafness.

Freytag (21) found, out of 18 members of five generations of a family, 11

instances of blue sclerotics and fragile bones, with hardness of hearing in addition in 6 of these. In 3 otherwise normal members, deafness was observed.

In 1922 Alexander (22) published the case of a boy aged $7\frac{1}{2}$ years with a history of repeated fractures and in whom there was marked blueness of the sclerotics. The mother of the boy also had deep blue sclerotics and defective hearing as well. The mother's sister, mother, and grandmother suffered from brittle bones, and in each case the sclera appeared pigmented.

Hall Stewart (23) in a later communication recorded a family of 10, in which the first four members, all females, had blue sclerotics. The eldest had sustained a fracture of the right femur on two occasions, and had suffered from partial deafness since childhood. This woman was married twice, and had by her first husband a girl, aged, at the date of the paper, 7 years, with blue sclerotics and a history of 12 fractures, and by her second husband a boy, 2 years, similarly affected, in hospital with a fractured femur. There was also a female infant, 5 months old, by the second husband, with blue sclerotics. The second sister had five children, one of whom, a boy, aged 7, had blue sclerotics and a record of 6 fractures of his leg bones. The other children appeared normal, as also did the three children of the third sister. The fourth sister died unmarried.

Description of an Oxford Family.

In the course of my duties as out-patient physician at the Oxford Eye Hospital, Mr. P. H. Adams, the hon. surgeon, pointed out to me a patient attending for mild conjunctivitis (No. 34) who possessed blue sclerotics. It is from this patient that the rest of the affected members have been traced.

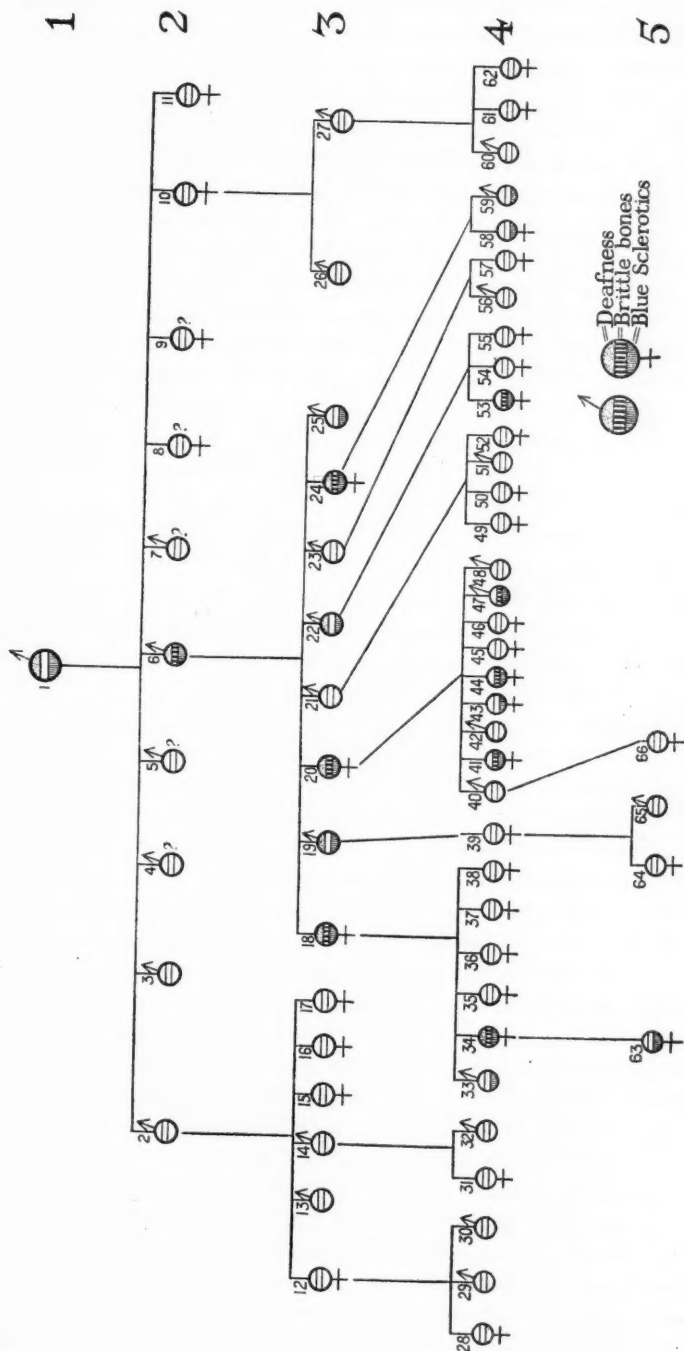
The majority of the family live in four small villages within a few miles of each other to the south-west of Oxford. The progenitor of this family resided in one of the villages, and very few of the descendants have migrated. Two members of the family, Nos. 43 and 44, are in domestic service in London and may come under notice there.

Most of the members of this family that have been interrogated have been eager both to give information and to submit themselves for examination. Some of the mothers of families have been interested to provide information that might lead to a solution of their family difficulties. The only real difficulty occurred in the case of a mother and daughter, the former stone deaf, but who could lip-read from the daughter, through whom questions had to be put; after some questioning, the daughter resolutely refused to allow further interrogation.

The family consists of 66 persons belonging to five generations (Fig. 1). Twenty-five members of the family, normal and affected individuals, have been seen, questioned, and examined.

Altogether, 18 members of the family, 8 males and 10 females (chart), are affected. It is possible that other members of the second generation described as having 'the same sort of eyes' might also be affected, but all such have been omitted from the list of positives. The tint of blue in the sclerotics has varied

THE OXFORD FAMILY


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from a deep porcelain blue tint to the just demonstrable blue of the infant which is abnormal in a child or adult. The tint sometimes is less vivid, and slaty-blue would perhaps best describe it. One case, not seen, is described as having eyes nearly black. In no case have any of the other features presently to be noticed, viz. brittle bones, deafness, been found in the absence of blue sclerotics.

The blueness of the sclerotics has not shown any relation to the grade of severity of the other symptoms. Blue sclerotics without evidence of fracture occurred in ten instances (6 males, 4 females). Blue sclerotics with fractures occurred in eight cases (2 males, 6 females). Blue sclerotics with deafness only occurred in four instances (3 males, 1 female).

Questions were put to elicit any other family failing or illness, but except for two instances of colour blindness (dichromatic) none was discovered.

Heredity. A reference to the family tree will show that the transmission of the features under review is direct from one generation to the next. There is no instance of a generation having been skipped. It is transmitted through both male and female, and no instance has come under notice in which an unaffected member has an affected descendant.

Eddowes noticed the hereditary character of the disease, and Burrows, Conlon, Cockayne, Freytag, and others pointed out the direct transmission. Hofmann was of the opinion that transmission occurred through the female, and Voorhoeve, who includes haemophilia as a feature sometimes seen in association, is obviously confusing two diseases, for haemophilia is now known to be transmitted only through the female.

Fractures. It has been mentioned that eight members had had fractures, two males and six females. Eighteen fractures occurred in seven patients, varying from seven to one in the same individual. The other affected member, not seen, was said to have broken 'nearly every bone in his body'. For the most part the fractures have affected the limbs. No history or suggestion was elicited pointing to deficiency or delay in healing.

The osseous system, however, shows further abnormalities. In No. 20 and No. 24 there is a considerable degree of kyphosis which commenced at 24 years of age. The father of these two members of the family is reported to have been markedly 'hump-backed', which deformity is stated to have come on gradually in early adult life. Certain writers, including Conlon, Harman, Cockayne, and Freytag, have laid stress on a diminution in stature and physique in the affected members; while others—for instance, Hermann, Ostheimer, Bronson, and Alexander—comment on an apparent alteration in the shape of the head, especially with regard to increase in size, the protuberance of the parietal bones, and the prominent frontal and occipital regions. Some of these latter characteristics appeared to be present in certain affected individuals in the Oxford family and had been noticed by friends. For example, No. 18 has a wedge-shaped head and was insistent that her father had a 'curious shaped head'. No. 33 was reported as having difficulty in getting a hat to fit him, and the size of his head was regarded as rather a joke in the family. The mother of No. 47 stated that

she could not get a cap to fit him and that her daughter had a very 'prominent back to her head'. The occipital region of No. 41 appeared distinctly prominent. The parietal and occipital bones of No. 47 and the frontal eminences of No. 53 were more than normally evident. In order to test the degree of abnormality in physical measurements, Mr. Dudley Buxton, M.A., Lecturer on Physical Anthropology in the University of Oxford, has kindly examined two adult males (Nos. 19 and 33), four adult females (Nos. 20, 24, 34, and 41), one male child (No. 47), and one female child (No. 53).

The measurements selected by him were those usually employed in anthropological work. The conclusions arrived at by him were that on the whole there appeared little reason to believe that the persons examined possessed heads which might not be found in the normal inhabitants of the neighbourhood. While it was true that the cranial measurements were well above the average, they were not necessarily abnormal, and the measurements obtained would certainly occur in any group which included 200 persons, and might occur in a smaller number. 'One patient (No. 41) showed certain features which would mark her off both from the rest of her family and from the inhabitants of any Oxfordshire village, but as these abnormalities only occurred in this instance, it is impossible to associate them with the disorder under review. The heads of the two children were possibly a little larger than those of many children of the same age, but no controls are at present available. From actual physical measurements the family appeared to include no particular type, but a range of types such as might be expected to occur in the neighbourhood of Oxford. A striking feature was the appearance of the iris in the patients examined. It seemed to lack the normal clearness and to present an almost "muddy" appearance. One of the causes of this may be an abnormal state of the cornea.

'It would not be accurate to say that a prominent occiput and a correspondingly long head is a characteristic. Some of the patients are much more brachycephalic than usual and in none is there a high degree of dolichocephaly.'

The teeth again show deficiencies: in No. 18 the enamel of the lower incisors was worn away, in No. 20 the teeth were described as showing holes and breaking away on biting bread, and a similar history of breaking off while eating was obtained in Nos. 24, 33, 41, 43. In three observed cases, Nos. 53, 58, and 63, the teeth are good.

Auditory deficiency. Deafness has occurred in 8 cases out of 17. The onset is in adolescence or early adult life, when the tendency to fractures diminishes. One member of the family (No. 18) is now completely deaf. None of the other members of the family with normal sclerotics show deafness.

Mr. Sydney Scott, Aural Surgeon to St. Bartholomew's Hospital, kindly examined four of the affected persons, Nos. 19, 20, 24, and 34, and two who were doubtful, Nos. 33 and 53. The deafness in the first four was due to otosclerosis. His report says: 'The similarity in these four patients' defect in hearing was very striking, although the degree of deafness differed considerably. In all four cases the tympanic membranes were intact, lustrous, and translucent,

and the inner tympanic wall reflected as a flamingo pink. The hearing tests were carried out with Bezold-Edelman continuous tones series of forks and whistles and with the steel monochord.

'Bezold's symptom triad was obtained, namely: (1) Low tone range limit raised from 16 d.v. to 24, 36, 55, 90, and higher in one or both ears. (2) Bone conduction better than air conduction by Rinne method Bezold A (118-75 d.v. per sec.). (3) Bone conduction prolonged.

'In two subjects these signs were alike, and there was little if any loss of appreciation of high tones; but in the other two members the loss of high tones was discoverable, and with these there was less prolonged hearing by bone conduction.

'In the case of No. 20 the asymmetrical difference in hearing was marked; the low tone limit being as low as 24 in the left ear, whereas it was nearly 90 d.v. on the right side; and one would not be justified in saying with certainty that the defect on the left side was otosclerotic from that side only.

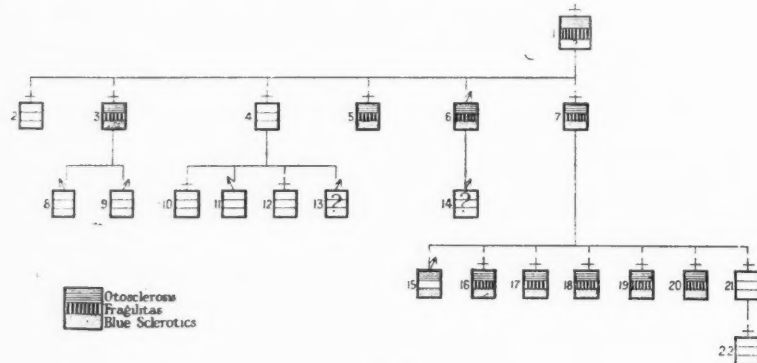


FIG. 2.

'In the case of No. 19 his replies to tests were too contradictory, and the only facts I could be certain of were: (1) that he was very deaf, (2) that he could not hear C_4 (2048 d.v.), (3) that he could not hear low forks by air conduction, but bone conduction was pronounced for Bezold A and C (256 d.v. per sec.).

'The condition of otosclerosis could not be diagnosed in the case of No. 53, the youngest member; the results of hearing tests were not sufficiently marked to justify the opinion that it was due to any permanent cause. Defective in acuity for watch and conversational voice, as her family had remarked, yet she could hear full tone-range from 16 d.v. to high notes produced by 16 cm. steel wire. Moreover, Rinne was still positive and Schwavach (bone conduction) was not prolonged. On the other hand she was always noticeably deaf.'

Adair-Dighton found nerve deafness in one of his patients. In Behr's cases the deafness was looked upon as of nerve origin; all the affected members of the family reported by van der Hoeve and de Kleyn suffered from otosclerosis. The chart of the family published by them is reproduced above.

X-ray examination of the labyrinth by Stenvers (17) in these cases is stated to have shown a covering of thin calcareous substance.

Seven individuals in the Currie family described by Bronson commenced to be deaf in early adult life and steadily became worse, but never totally deaf. Three of the patients with deafness were examined by Fraser, who found in two instances otosclerosis, and in the third otosclerosis with nerve deafness in addition.

Four of Voorhoeve's patients suffered from labyrinthine deafness. The incidence of deafness among the normal individuals in the families of Freytag and of Blegvad and Haxthausen has already been referred to.

One member in each of the families published by Alexander and Hall Stewart suffered from deafness.

Notes on the Oxford family.

Generation 1.

No. 1. Male, died in old age, reported to have been deaf and to have had blue sclerotics; date of onset of deafness unknown. No history of fractures.

Generation 2.

No. 6. Male, died at the age of 63, blue sclerotics, became deaf when a young man, 'broke nearly every bone in his body'. 'Curious shaped head.'

Generation 3.

No. 18. Female, aged 49, blue sclerotics, became deaf at 13, now quite deaf. 'Wedge'-shaped head, fractured leg when aged 4. Sigma test for syphilis negative. Inclined to fall about from attacks of giddiness. Enamel of lower incisors worn away.

No. 19. Male, aged 47, blue sclerotics, became deaf in his teens, no fractures. Mr. Sydney Scott reports: 'Very deaf indeed, but an unreliable witness. Tympanic membranes intact, marked flamingo-pink reflex. Cannot hear C₄ though very loud. Obviously bone conduction greater than air, but low limit unascertainable. Probably otosclerosis advanced degree.'

No. 20. Female, aged 45, blue sclerotics, slightly deaf; when 9 sustained a fracture of the humerus; feels giddy frequently. The X-ray report is referred to on p. 285. Embryontoxon (juvenile arcus senilis) present. Teeth 'used to go into holes and break on pieces of bread'. Was unable to nurse any of her children beyond the ten days she was in bed, owing to violent pain in the back and chest and shortness of breath on attempting to do so. The pain was so bad that she was unable to sit up in bed or get out of bed unless she rolled out, and it completely doubled her up when standing. The pain passed off gradually within a week or two of weaning.

Mr. Sydney Scott's report:

Very deaf for voice in right ear.
Can hear conversation, raised voice, in left ear.
She places hand to left ear, and did not seem to realize she was so deaf as she is in the right ear.
Tympanic membranes flamingo-pink reflex.
Otosclerosis, right ear.
Defect in hearing, left ear.
Possibly otosclerosis without fixation of stapes.

Bezold Fork.

Low Limit.

<i>Right.</i>	<i>Left.</i>
90	24
55	16

Monochord.

Bone cond.	14 cm.	14 cm.
	24 cm.	24 cm.
Weber		
Rinne	—	—
Sch.	+	+

No. 22. Male, died in war, aged 37, blue sclerotics 'nearly black', became deaf when a young man, no history of fractures.

No. 24. Female, aged 29, slaty-blue sclerotics, became deaf gradually between 14 and 15. Broke leg and dislocated shoulder. Thyroid slightly prominent, hirsuties on chin. At 17 years teeth 'began to come into holes in the middle and broke right off'.

Mr. Sydney Scott's report:

Can lip-read, cannot hear except loud voice close to ear.

Tympanic membranes intact.

Flamingo-pink reflex.

Diagnosis:

Otosclerosis.

Bezold Fork.

Low Limit.

Right. Left.

55 d.v. 55 d.v.

36 36

Monochord.

High Limit.

43 50

16 16

Rinne

— —

Schwavach

+ +

No. 25. Male, died at 4 years, blue sclerotics, no fractures or deafness.

Generation 4.

No. 33. Male, aged 28, blue sclerotics, large head, embryotoxon present. Eye grounds normal, divergent strabismus due to an error of refraction.

Had all his teeth extracted as 'bits kept breaking off'. Examination of ears (Mr. Sydney Scott): Normal, deafness caused by wax.

No. 34. Female, aged 27, broke her arm when 9 and her leg when 16. Embryotoxon present. Transillumination more brilliant than normal. Sigma test for syphilis negative. Upper and lower incisors slightly chipped at edges; often feels giddy and has been getting deaf for past two years. See Plate 18.

Mr. Sydney Scott's report:

Tympanic membranes intact.

Flamingo-pink reflex.

No wax.

Otosclerosis present.

Bezold Fork.

Low Limit.

Right. Left.

36 d.v. 36 d.v.

24 d.v. 24 d.v.

Monochord.

High Limit.

Air cond. 24 cm. 30 cm.

Bone cond. 16 cm. 16 cm.

Rinne — —

Sch. + +

No. 41. Female, aged 23, blue sclerotics, 7 fractures, not deaf, eye grounds normal. Transillumination obviously more brilliant than normal. Twelve teeth missing as a result of breaking off whilst eating.

No. 43. Aged 18, blue sclerotics, no breaks, no deafness. Statement of mother that she has a 'very prominent back to her head', subsequently verified. Teeth 'go into holes and break off'. Examination of ears (Mr. Sydney Scott): Hearing tone range and acuity for all tones normal.

No. 44. Female, aged 16, blue sclerotics, has broken a leg. Not deaf.

No. 47. Male, aged 6, blue sclerotics, 4 fractures before 4 years of age, not deaf, prominent parietal and occipital bones. Slight embryotoxon. X-ray report, p. 285.

No. 53. Female, aged 10, blue sclerotics, prominent frontal bones, history of fractured leg, slight exophthalmos, always noticeably deaf. Mr. Sydney Scott reports that the condition of otosclerosis could not be diagnosed. Teeth good.

No. 58. Female, aged 1½ years, blue sclerotics, teeth good, not deaf.

No. 59. Male, born 12 June 1923, blue sclerotics.

Generation 5.

No. 63. Female, aged 8 months, blue sclerotics, teeth good, apparently not deaf.

Aetiology and Pathology.

This is discussed at length by Bronson. In J. D. Rolleston's patient congenital syphilis was present, but it was regarded as uncertain whether the fragilitas could be looked upon as due to that cause or to some constitutional peculiarity.

In Behr's patient there were also signs of congenital syphilis, but this was considered not to be a direct cause, though it might have aggravated the 'congenital weakness of the affected tissues'. The blood serum reaction of two of his patients was negative, as it was also in Langmead's and Ostheimer's cases.

In the present series the Dreyer-Ward (sigma) reaction was negative in the two patients whose serum was tested—No. 18 in generation 3, and No. 34 in generation 4. There was no clinical indication of any syphilitic taint in any of the individuals seen and further blood examinations were deemed unnecessary. In the absence of post-mortem evidence any theory is highly speculative.

Buchanan (24) made a histological examination of an eye from a girl aged 9, who sustained an injury to the left eye which necessitated its removal. It was observed that the patient's other eye had a bright blue-coloured sclerotic which gave the impression of being very thin. The parents of the child were certain that the whites of both eyes had been of an unusual blue colour since birth. The scleral coat of the affected eye was about $\frac{1}{3}$ of the normal thickness and the cornea was also much thinner than usual. Microscopically the fibres of the cornea and sclera appeared about the normal size but were abnormally few in number. The anterior elastic lamina was completely absent.

As no mention is made of an hereditary element in the history, Conlon considers that this case should not be regarded as belonging to the syndrome. And as no history of fracture is recorded, Bronson holds a similar view. A like objection can be raised to the case described by her in which an infant aged 11 months, with typical blue sclerotics, showed, on examination of one of the eyes, a sclera of normal thickness with the size and number of the fibres normal for the age of the child.

Bronson considers the sclerotics to be abnormally translucent rather than decreased in thickness, which was the view held by Peters and also by Harman.

Herrman thought that the lack of lime salts was responsible for the transparency of the sclera and iris and for the lack of density in the bones and connective tissues generally. That the defect is probably in the mesoblastic tissues of the body is the opinion of Cockayne, of Hofmann, who adduced evidence from the comparative anatomy of fishes and reptiles in support of the hypothesis, and also of Blegvad and Haxthausen. As manifestations of this inferiority of the mesenchyme, Voorhoeve described the association of (*inter alia*) cleft palate, spina bifida, and congenital heart disease with the scleral and osseous changes.

How far a deficiency in the endocrine system may be responsible, it is at present impossible to say, but the appearance of the patients constantly brings this idea forward. Behr describes bulging of the cornea in association with blue sclerotics, and Mr. P. H. Adams tells me that in cases of conical cornea he has had the impression for several years that there may be a defect in the internal secretions. Certain cases of keratoconus seen at the Oxford Eye Hospital suggest this aetiology strongly. They present overgrowth of hair on chin and breasts, a yellow waxy skin, and a premature wearing away of the teeth.

It may only be a coincidence that case No. 24 had an enlarged thyroid gland with a growth of hirsuties on the chin, and that No. 53 showed a slight but definite degree of exophthalmos. Of case No. 47 it was stated that between the ages of 8 and 12 months he used to wake up with attacks of what are called by his mother 'asthma', in which he 'went stiff all over'. It is to be presumed that these attacks were of the nature of tetany. The association of zonular cataract with defective enamel of the permanent teeth is well recognized (25). Zonular cataract may follow a prolonged attack of tetany (26), and may be accompanied by various skin lesions simulating pemphigus (27). Tetany cataract has been produced experimentally in rats by parathyroidectomy, and in these animals, after removal of the parathyroids, also occurred defects in the enamel of the teeth (28).

Zonular cataract is reported by Blegvad and Haxthausen, who also describe a macular skin condition with atrophy, chiefly of the elastic fibres of the conium.

It is perhaps noteworthy that Eddowes's patient of 1900 suffered from eczema.

Late development of the teeth is mentioned by Crocco (29) as occurring in conjunction with other lesions. The prevalence of marked enamel defects in the teeth of several members of the Oxford family has already been commented on. A possible explanation of these phenomena may be a disturbance of function of the parathyroids with an alteration in the calcium metabolism.

That otosclerosis may be a manifestation of a dietary deficiency still existing during adult life is the conclusion arrived at by Kauffman, Creekmur, and Schultz (30) following feeding experiments on rats where fat-soluble A and calcium were omitted. The occurrence of normal and affected individuals in the same families living under similar conditions makes the possibility of

dietary deficiency very unlikely in this series. The influence of an alteration in the supply of lime salts is discussed above.

X-ray Examinations.

In Behr's patient numerous X-ray pictures showed no decided change in the bones except a slight thickening of a rachitic nature at the rib angles. The slight atrophy in the trabeculae of the tarsus and lower end of the tibia which was found was not considered positive enough to lay any stress on.

Langmead's child is stated to have had bones very delicate in construction and unusually translucent to X-rays.

In Cockayne's series no evidence of rickets was found on X-ray examination. The middle of the shafts of the long bones showed an abnormal amount of compact bone, but towards the extremities they appeared to be more transparent than usual.

In the case of Herrman's boy the bones and surrounding soft parts are stated to have lacked density in comparison with a control of the same age. The bones of the forearm in Freytag's patients are reported to have appeared more delicate in structure than normal.

X-ray photographs published with Hall Stewart's paper showed the cortex of the bone excessively thin and the medulla somewhat diffuse.

In this series, case No. 20, a woman of 45, and case No. 47, a boy of $6\frac{1}{2}$, were examined by Mr. R. H. Sankey, Honorary Radiographer to the Radcliffe Infirmary, Oxford. His reports read—Case No. 20: 'The shaft of the humerus looks fragile, especially in the region of the neck.' Case No. 47: 'Density of the femora and tibiae? not up to standard of age.'

In the absence of a large number of control examinations it is manifestly impossible to make accurate deductions from the comparatively few X-ray photographs that have been taken.

The reports which have been published suggest that the bones are rather more delicate in construction than usual.

Conclusions.

1. Another family is published in which the syndrome of blue sclerotics, fragile bones, and otosclerosis is present.
2. The exact cause of the syndrome and its pathology is at present uncertain.
3. The anomalies are inherited and are directly transmitted.
4. The deafness is not present at birth, but for some unknown reason begins to manifest itself in the second or third decade.
5. The disorder does not appear to shorten life in any way.

I desire to express my sincere thanks to Sir Archibald Garrod, Regius Professor of Medicine in the University of Oxford, for his constant assistance,

without which the very valuable expert opinions would not have been obtained. I have much pleasure also in thanking Mr. P. H. Adams for the ophthalmological examinations, Mr. R. H. Sankey for the X-ray reports, Dr. W. T. Collier, Honorary Assistant Physician, Radcliffe Infirmary, for the reports on the blood sera, and Mr. Minn, Engineer at the Clarendon Press, for all the trouble he took over the colour photograph. To Mr. Sydney Scott, who paid a special visit to the Berkshire village for the purpose of determining the cause of the deafness, and to Mr. Dudley Buxton for a similar kindness in regard to physical measurements, I am under a deep debt of gratitude. Finally I wish to acknowledge the adoption of many suggestions made by Dr. A. G. Gibson.

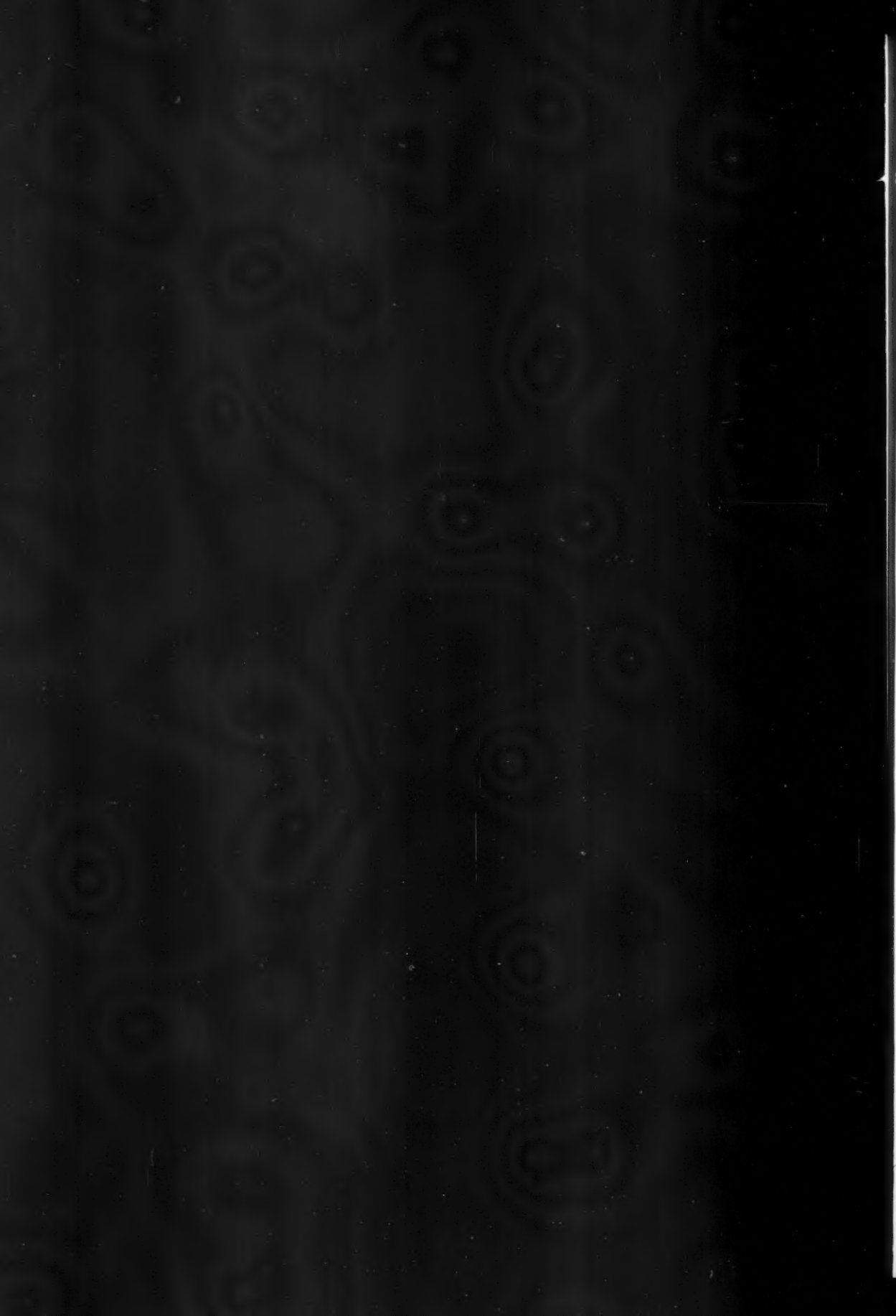
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REPRODUCTION BY COLOUR PHOTOGRAPHY
OF CASE NO. 34



THE INORGANIC PHOSPHORUS CONTENT OF CEREBRO-SPINAL FLUID

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THIS investigation was undertaken to determine the inorganic phosphorus (inorg. P.) content of the cerebro-spinal fluid: (a) in the normal subject; (b) in disease, especially degenerative lesions of the central nervous system.

The influence of such factors as the inorganic phosphorus content of the plasma, the age of the subject, &c., on the inorg. P. content of cerebro-spinal fluid has also been considered.

1. *Historical.*

Of the products of the hydrolysis of lipoids *in vitro*, choline has received most attention as an index of nerve-tissue degeneration. Both the blood and cerebro-spinal fluid of patients suffering from chronic nervous lesions have been subject to analysis from this point of view.

Considerably less work has been carried out on the phosphate content of cerebro-spinal fluid as an index of nerve-tissue degeneration. Among those who have directed their attention to this aspect of the subject are Krainski (1), Donath (2), Nonne and Apelt (3), Apelt and Schumm (4), de Buck (5), and Forbes (6).

The results obtained by these workers differ considerably from each other; e. g., in normal fluids, Donath found 2.39 mg. inorg. P. (5.4 mg. P_2O_5), de Buck found 4.87 mg. inorg. P. (11 mg. P_2O_5), whilst Schumm found 1.93 mg. inorg. P. (4.4 mg. P_2O_5). In various pathological states, widely different values are given by these earlier workers.

Donath reports an increase in such conditions as epilepsy, G.P.I., cerebral tumour; even hysteria and neurasthenia are said to be accompanied by a definite increase in the phosphate content of cerebro-spinal fluid. On the other hand Apelt and Schumm found no rise in any of their cases of nervous disease (including two of tuberculous meningitis). Their highest value was found in a case of uraemia, and this caused them to doubt the value of an increase of phosphate as a sign of nerve degeneration. Mestrezat (7) summarized the work on the phosphate content of the cerebro-spinal fluid thus:

[Q. J. M., April, 1924.]

'Il est difficile dans l'état actuel de nos connaissances de décider parmi ces résultats contradictoires.' He suggests that the phosphate content of cerebro-spinal fluid is dependent on that of the blood, rather than on the disintegration of nervous tissue.

The explanation of the varied results obtained by different workers is to be found: (i) in the methods used to estimate phosphorus; (ii) in the fact that insufficient attention has been given to the differentiation of total P., organic P., and inorg. P.

Donath, for example, used Neumann's method, estimating the total phosphorus as phosphomolybdate and subtracting from this the amount of phosphorus calculated to be present in the protein of cerebro-spinal fluid, a method obviously inaccurate. A reinvestigation of the subject was suggested by the recent descriptions of accurate methods for the estimation of inorganic phosphorus in small amounts.

2. Method.

Briggs's modification of the Bell-Doisy method (8), with slight alterations, was found, after comparison with the methods of Bloor (9) and Tisdall (10), to combine accuracy and convenience. In order that the results obtained be strictly comparable the same technique has been used in all the cases included in this paper.

To 2 c.c. of cerebro-spinal fluid add 6 c.c. of water and 2 c.c. of 20 per cent. trichloroacetic acid. Shake vigorously and allow to stand for ten minutes. Filter through an ash-free paper. Prevent evaporation by covering the funnel with a watch-glass.

A standard solution of dry KH_2PO_4 is prepared containing 2.5 mg. of P. per 100 c.c. Deliver 5 c.c. of this standard solution and 5 c.c. of the filtrate into separate test-tubes and to each add 2 c.c. of the molybdate solution,¹ 1 c.c. of a 40 per cent. solution of sodium sulphite in water, and 1 c.c. of a freshly-prepared solution of hydroquinone.² Allow to stand for one hour and then compare in a colorimeter (the 'Kober' was used in these estimations).

The above procedure has been tested in many ways. Duplicate determinations on the same fluid made by another observer³ were always within 5 per cent. of my own. Added phosphate could be recovered with an accuracy of ± 3 per cent.

Great care must be taken to prevent turbidity in the final solutions by vigorous shaking of the fluid after adding the protein precipitant, especially where protein is present in excess, for though a clear filtrate be obtained, protein may be present in it, unless the above precaution be taken, and is precipitated by the acid molybdate solution. The colorimeter cups and piston must be cleaned before each determination, especially if the same colorimeter has been used for

¹ Dissolve 25 grm. of ammonium molybdate in 300 c.c. water and then add 200 c.c. of 37½ per cent. H_2SO_4 .

² Dissolve 0.5 grm. hydroquinone in 100 c.c. water and add 1 drop of conc. H_2SO_4 .

³ Dr. L. Cunningham.

sugar or non-protein nitrogen estimations in which phosphomolybdic acid or Folin's acid digestion mixture is used. A standard solution of 1.5 mg., 2 mg., or 2.5 mg. of inorg. P. per 100 c.c. made no practical alteration in the readings from a given fluid. All fluids were examined as soon as possible after withdrawal, usually within three hours.

3. Results.

The following results have been obtained from over 150 examinations; all are expressed in mg. of inorganic phosphorus per 100 c.c. of cerebro-spinal fluid.

1. *Normal* (i.e. patients showed no signs of organic nerve lesion). 1.50; 1.52; 1.74; 1.80; 1.90; 1.66; 1.72; 1.67; 1.60; 1.65; 1.39; 1.68; 1.54; 1.39; 1.71; 1.75; 1.75; 1.87; 1.60; 1.55; 1.85; 1.79; 1.69; 1.36; 1.81; 1.79; 1.65; 1.79; 1.39; 1.54; 1.39; 1.69; 1.45; 1.71; 1.25; 1.75; 1.52; 1.84; 1.82; 1.63; 1.66. (41 cases, average 1.64.)

2. *Epidemic encephalitis (lethargica)*.

(a) *Acute*. 1.76; 1.98; 1.76; 1.62; 1.52; 1.69; 1.65; 1.90; 1.66; 1.48; 1.66; 1.47; 1.29; 1.61; 1.50; 1.50; 1.52; 1.52. (16 cases, 18 fluids; average 1.62.)

(b) *Chronic*. 2.00; 2.19; 1.61. (2 cases, 3 fluids; average 1.97.)

3. *Meningitis*.

(a) *Tuberculous*. 2.94; 2.81; 2.45; 2.12; 1.92; 3.43; 2.60; 2.87; 2.55; 2.40; 2.03; 2.84; 2.40; 2.78; 2.05; 1.91; 2.48; 3.12. (16 cases, 18 fluids; average 2.54.)

(b) *Meningococcal*.

Case I, 2.08; 2.40; 2.80; 2.63; 2.50; 2.91; 2.84; 3.37; 3.21; 4.34.
Case II, 3.3; 3.12. Case III, 1.69; 2.22; 2.36; 2.40. (3 cases, 16 fluids.)

(c) *Syphilitic*. 2.47.

(d) *Influenzal*. 1.83.

4. *General paralysis*. 1.93; 2.23; 2.02; 1.66; 1.66. (5 cases, average 1.9.)

5. *Tubes*. 1.8; 1.95; 1.85; 1.99; 1.97; 1.52; 1.79; 1.80; 2.00; 1.84. (10 cases; average 1.86.)

6. *Disseminate sclerosis*. 1.84; 2.07; 1.85; 1.38. (4 cases; average 1.79.)

7. *Compression myelitis*. 2.00; 2.02; 2.12. (3 cases; average 2.04.)

8. *Epilepsy* (no cause found). 1.79; 1.92; 1.52. (3 cases; average 1.74.)

9. *Neurosyphilis*. 1.91; 1.93; 1.66; 1.74; 1.60; 2.00; 2.21 (hydrocephalus). (7 cases; average 1.86.)

10. *Hemiplegia* (old standing—thrombotic or haemorrhagic in origin—no neurosyphilis). 1.87; 1.98; 1.50; 1.56. (4 cases; average 1.73.)

11. *Cerebral tumour*. 1.75; 2.30 (glioma in 3rd ventricle); 1.96; 1.47; 1.67; 2.07; 1.48. (7 cases; average 1.81.)

12. *Recent cerebral haemorrhage* (i.e. patient died within 24 hours from onset of lesion). 1.52; 1.69. (2 cases; average 1.61.)

13. *Spastic paraplegia* (cause unknown). 2.17 ; 1.95 ; 2.23 ; 1.92. (4 cases ; average 2.07.)

14. *Miscellaneous.* Frontal abscess 1.54.

Hydrocephalus (not syphilitic) 1.85.

Chronic progressive ophthalmoplegia 1.65.

Cerebral embolism (infective endocarditis) 1.65.

T.B. caries with paraplegia (? compression) 1.52.

15. *Post-mortem specimens.* Ten estimations were carried out.

The results varied from 5.41 mg. in a fluid obtained three hours after death to 14.8 mg. in a fluid obtained twenty hours after death.

The important facts which emerge from an examination of the above results are :

1. The inorg. P. content of cerebro-spinal fluid in the normal subject lies between 1.25 and 2.00 mg. per 100 c.c. of fluid.

2. In 16 cases (18 fluids) of acute epidemic encephalitis no variation from the normal was found.

3. In 16 cases of tuberculous meningitis, 88 per cent. (14 cases) showed abnormally high values (greater than 2 mg.) on the first examination ; the remaining two cases showed 1.90 and 1.92 mg. per cent. respectively ; a fluid obtained on a subsequent date from the former of these two patients showed 2.48 mg. per cent. Thus of 16 cases examined 15 showed a definite increase of inorg. P. In six of these (38 per cent.) the tubercle bacillus was found in the cerebro-spinal fluid. The diagnosis was confirmed by autopsy in all cases but one in which permission was refused. This increase of inorganic P. in tuberculous meningitis would appear of diagnostic importance in differentiating this condition from epidemic encephalitis (see Fig. 1).

4. In meningococcal and acute syphilitic meningitis the cerebro-spinal fluid was found to contain an excess of inorg. P. In one case of meningococcal meningitis the cerebro-spinal fluid was examined on ten consecutive occasions, in another on four occasions ; both these cases showed a tendency to increasing inorg. P. content of the cerebro-spinal fluid as the lesion advanced.

One fluid from a case of influenzal meningitis was very purulent, but the inorg. P. was only 1.83 mg. per cent. (One case of pneumococcal meningitis in which the cerebro-spinal fluid content of inorg. P. was estimated by the Tisdall method gave less than 1.8 mg. per cent. inorg. P.)

5. One case, only, showed less than the lowest normal—a central pneumonia with meningismus. The cerebro-spinal fluid was under considerable pressure and contained only 1 mg. per cent. (repeated on three specimens). The boy, aged 14 years, recovered in a few days.

6. The average inorg. P. content of the cerebro-spinal fluid from cases of chronic organic nerve disease is 1.83 mg. per cent., a value slightly higher than the average of normal fluids—1.64 mg. per cent.

4. *The Influence of Various Factors on the Inorganic Phosphorus Content of Cerebro-spinal Fluid.*

A. *The inorg. P. content of blood-plasma.* To ascertain what relationship, if any, exists between the plasma and cerebro-spinal fluid with regard to their content of inorg. P., blood and cerebro-spinal fluid were withdrawn from 17 patients, in the fasting condition, and the inorg. P. determined in each. The following table and Fig. 2 show the results.

TABLE I.

Cases.		Mg. of Inorg. P. per 100 c.c. of	
		Blood.	C.S.F.
1	Normal	2.77	1.39
2	Normal	3.87	1.54
3	Normal	3.42	1.60
4	Normal (gumma of testis)	4.08	1.87
5	Normal	3.18	1.85
6	Normal	2.30	1.25
7	Encephalitis, epidemic	4.15	1.65
8a	Encephalitis, epidemic	6.31	1.76
8b	Encephalitis, epidemic	3.46	1.98
8c	Encephalitis, epidemic	3.41	1.76
9	Acute syphilitic meningitis	2.77	2.47
10	Tabes dorsalis	3.51	1.80
11	Taboparesis	4.17	2.02
12	Spastic paraplegia	5.00	2.23
13	Spastic paraplegia	4.54	2.19
14	Spinal caries and paraplegia	3.40	1.52
15	Old hemiplegia	5.30	1.50
16	Cerebral tumour	5.00	1.96
17	Chronic epidemic encephalitis	3.97	2.19

From the above table it will be seen that there is no constant relationship between the inorg. P. of blood plasma and cerebro-spinal fluid; whilst the inorg. P. content of cerebro-spinal fluid is approximately half that of the plasma, a well-marked rise in the plasma shows no corresponding rise in the cerebro-spinal fluid, and, as is especially well seen in the case of acute syphilitic meningitis (No. 9), a definite increase of inorg. P. in the cerebro-spinal fluid is unaccompanied by any corresponding increase in the plasma.

In view of the close relationship between calcium and phosphorus in human blood the recent work on calcium in the cerebro-spinal fluid may here be noted. Halverson and Bergeim (11) and Leicher (12) find it markedly constant—4.7 to 5.4 mg. per cent.—i. e. slightly less than half the amount of calcium in serum. Leicher could find no relation between the amount of calcium present in the serum and cerebro-spinal fluid.

B. *Age of patient.* It has been shown that before the cessation of bone growth at 20 years of age, the plasma inorg. P. is 5 to 6 mg. per cent., whilst after 20 years of age there is a decrease to 3–4 mg. per cent. except during the union of fractures, when there is again a rise to 5 mg. per cent. (13).

Age does not, however, affect the cerebro-spinal fluid content of inorg. P. Six children below 14 years had an average of 1.63 mg. per cent., whilst 35

adults above 20 years had an average of 1.64 mg. per cent. Age alone then is insufficient to account for a rise in the inorg. P. in the cerebro-spinal fluid. Moreover, a glance at the following table shows that in cases of tuberculous meningitis the rise is independent of age.

TABLE II.

Age of Patient.	Mg. of Inorg. P. %.
34 years	2.94; 2.81
9 "	2.12; 2.48
8 "	2.84
6 "	2.48
3½ "	2.4
3 "	2.03
2½ "	1.92

C. *Cell and protein content of the cerebro-spinal fluid.* Neither of these factors is sufficient to explain the rise observed in meningitic cases, for many fluids containing a marked increase of cells and protein showed little or no increase of inorg. P. in the cerebro-spinal fluid. Thus a case of influenzal meningitis—the most purulent fluid examined—and a case of frontal abscess in which there was a marked increase of cells and protein showed no increase in inorg. P. Conversely, the rise found in meningitis bore no relationship to the cell content of the fluid.

Centrifugalizing the cerebro-spinal fluid to remove the cells did not alter the inorg. P. content, within the limits of experimental error, of ten fluids from cases of tuberculous meningitis, thus showing that there is no discharge of phosphates from the cells as a result of precipitation with trichloroacetic acid.

D. *Proximity of death.* Attention has been drawn above to the marked increase of inorg. P. in cerebro-spinal fluid withdrawn after death. It was thought that as the cases of tuberculous meningitis invariably succumbed the observed increase in these cases might in some way be connected with the approach of death.

This was disproved by two facts:

(i) Conditions other than meningitis show no increase of inorg. P. in cerebro-spinal fluid even a few hours before death; e.g. a case of epidemic encephalitis, from which cerebro-spinal fluid was obtained six hours before death, showed 1.66 mg. per cent.; two cases of cerebral haemorrhage—three and four hours before death—respectively 1.69 and 1.52 mg. inorg. P. per cent.

(ii) In cases of tuberculous meningitis no relation between the inorg. P. of the cerebro-spinal fluid and the duration of life after lumbar puncture was found, as the following table shows:

TABLE III.

	Duration of Life after Lumbar Puncture.	Mg. of Inorg. P. %.
I	8 days	2.55
II	7 "	1.92
III	8 "	2.84
IV	3 "	2.40
V	4 "	2.03
VI	1 "	2.12

The increasing amount of inorg. P. which accompanies an advancing meningitic lesion cannot, therefore, be explained by the gradual approach of death.

E. *Repeated lumbar puncture.* That the increase is not due to the effect of repeated lumbar puncture is shown by the fact that, apart from advancing meningitic lesions, repeated puncture does not cause an increase in the inorg. P. content of cerebro-spinal fluid; e.g. a case of epidemic encephalitis, from whom fluid was withdrawn at intervals of a week, showed over a period of three weeks 1.76, 1.98, and 1.76 mg. per cent.

F. *Bacterial activity.* The available data afford no evidence for the conversion of organic P. into inorg. P. in meningitis as a result of bacterial activity. It is interesting to add in this connexion that in the meningococcal cases the inorg. P. was found to bear no relation to the number of organisms present, and that in two cases of meningitis—influenzal and pneumococcal—although organisms were present in abundance, no increase of inorg. P. was found in the cerebro-spinal fluid. The growth of coliform bacilli in cerebro-spinal fluid is often accompanied by a diminution of inorg. P.

5. Discussion.

Two other factors must be considered in attempting to explain any rise in the inorg. P. content of cerebro-spinal fluid observed in disease: (i) the degeneration of nervous tissue with a resulting liberation of P. in inorganic form; (ii) alteration in the permeability of the choroid plexus in diseased states.

A. *Degeneration of nervous tissue.* Our inability to detect any appreciable increase in the inorg. P. content of cerebro-spinal fluid from patients with chronic progressive degenerative nerve lesions renders necessary a consideration of some recently available data.

1 gm. of lecithin contains approximately 40 mg. of P. (17). Brain-tissue contains approximately 6 per cent. of phosphatides calculated as lecithin in fresh tissue (18). The sudden and complete disintegration of 1 gm. of nerve-tissue would yield 2.4 mg. of inorg. P., which, if diffused through the cerebro-spinal fluid—normally, say, 150 c.c.—would increase the inorg. P. content of cerebro-spinal fluid by 1.6 mg. per cent. When one considers (i) the rapidity of drainage from cerebro-spinal fluid to blood (14, 15, 16); (ii) the small amount of nervous tissue which undergoes degeneration; (iii) the slow rate of degeneration (often years); and (iv) that complete disintegration to free phosphate ions is necessary before the phosphorus can be estimated as inorganic, it is not difficult to understand the absence of an increase of inorg. P. in the cerebro-spinal fluid in chronic nervous disease as a result of tissue break-down.

Moreover, even in acute epidemic encephalitis, where the rate of nerve-tissue involvement is rapid, no increase in the inorg. P. of cerebro-spinal fluid is found. The above observations render extremely improbable the view that the increased

inorg. P. found in acute tuberculous, meningococcal, and syphilitic meningitis is due to an accompanying encephalitis.

There is little doubt that autolysis of the nervous tissue explains the marked increase in the inorg. P. content of cerebro-spinal fluid after death. Here values far exceeding those normally present in blood are obtained, and would seem to depend on three facts: (i) that the circulation has ceased; (ii) that the nervous system undergoes autolysis *en masse*: thus a large amount of nervous tissue is involved; and (iii) that the H ion of cerebro-spinal fluid is increased after death.

The last fact merits further comment. The average pH of cerebro-spinal fluid under normal conditions varies between 7.4 and 7.9 (19). Parsons and Shearer (20) give a value as low as 7.2-7.3. Normal tissues have the same pH as the blood, i.e. $7.4 \pm$ (21), and as long as this is maintained, Bradley has shown that there is no evidence that autolysis can go on, either *in vitro* or *in vivo*. Alteration in the reaction of the tissue profoundly affects both the speed and extent of autolysis. If a tissue be kept alkaline or neutral, autolysis is practically nil; if a tissue be made acid, autolysis readily proceeds; in fact, Bradley (21) states that 'it is certain that most of the substances studied which do accelerate autolysis do so by virtue of their acidity'. After death, due, probably, to the production of lactic acid and acid from tissue fats, the H-ion concentration of tissues is markedly increased. Morse (22), using the indicator method, found a rapid rise from pH 7 to pH 6, which was reached in five days, whilst Dernby (23), using the potentiometer method, found that the acidity developed rapidly, and within twenty-four hours the pH of a tissue mixture was $6.5 \pm$. There is thus ample evidence that the conditions present after death are favourable for tissue autolysis. The literature shows surprisingly few observations on the H-ion concentration of cerebro-spinal fluid during life. The most important observations are those of Levinson (24) and Parsons and Shearer (20). No alteration is said to be found in such conditions as 'tuberculous meningitis, lateral sclerosis, and neurosyphilis'. In meningococcal meningitis, however, pH is lowered (25, 26), but is always on the alkaline side of neutrality; thus it does not promote tissue autolysis, and during life is not responsible for the increased inorg. P. found in the cerebro-spinal fluid in this disease.

It is of interest to compare the above facts with the ultimate conclusions of Sir Frederick Mott on the presence of choline in the cerebro-spinal fluid.

In his Oliver-Sharpey Lectures on the Cerebro-spinal Fluid (27) he summarizes his own and Halliburton's work on choline in the cerebro-spinal fluid thus:

'Professor W. D. Halliburton and I made a number of observations tending to show that choline occurs in the blood and cerebro-spinal fluid in conditions where a large amount of nervous tissue was undergoing degeneration. The existence of choline was demonstrated by physiological and microchemical tests. I am, however, of opinion from further observations that the microchemical tests employed—i.e. the formation of choline platino-chloride crystals—were unreliable and that the crystals we obtained were more often potassium and ammonium salts; moreover, a number of *post mortem* fluids were used for our observations,

and in the laboratory we have found, using the periodide test, that a very small quantity of fluid obtained from any *post mortem* within a comparatively short time of death gives the test denoting the presence of choline or some substance from which choline is easily dissociable. We have been unsuccessful in obtaining the test in fluids obtained during life even in cases of general paralysis.'

Further evidence of post-mortem autolysis is found in the non-protein nitrogen content of cerebro-spinal fluid, normally 20-30 mg. per cent. Some hours after death I have found amounts varying from 200 to 400 mg. per cent.

B. *Altered permeability of the choroid plexus.* The cells of the choroid plexus form a barrier between the blood and cerebro-spinal fluid. We have thus two liquids separated by a partially permeable membrane. But this membrane is living and its permeability 'selective'. Thus, whilst phosphates are present in greater quantity in the blood than in the cerebro-spinal fluid, the chlorides are present in greater quantity in the cerebro-spinal fluid than in the blood; moreover, some substances, e. g. fibrinogen, are normally absent from the cerebro-spinal fluid.

In meningitis the chemical changes which occur in the cerebro-spinal fluid are of four types:

1. *An increasing concentration in the cerebro-spinal fluid of those substances which are normally present in greater quantity in the blood.* The increased protein content of meningitic fluids has long been recognized. The well-marked increase in inorganic phosphorus is shown above.

Fabris (28) has shown recently that in tuberculous meningitis the cholesterol content of the fluid is increased. An apparent exception to this rule is the marked diminution of glucose which occurs in meningitis. Here, however, the utilization of this assimilable food-stuff by organisms and cells present in the fluid complicates the problem.

2. *A decreasing concentration in the cerebro-spinal fluid of those substances which are normally present in greater quantity in the cerebro-spinal fluid.* This is strikingly seen in the chloride content of cerebro-spinal fluid, which is normally 700-760 mg. per 100 c.c.; the chloride content of blood-plasma being normally 570-640 mg. per 100 c.c. (29).

Mestrezat (7) has shown that in the meningitides, especially tuberculous meningitis, a definite and marked diminution of chlorides in the cerebro-spinal fluid occurs, though in the early stages there may be no reduction. A chloride content of cerebro-spinal fluid below 680 represents a grave meningeal infection. In my own series of cases the lowest chloride value found was 590 mg. per cent. I have not yet encountered any cases of meningitis in which the chlorides of the plasma have exceeded those of cerebro-spinal fluid, nor, conversely, any similar case in which cerebro-spinal fluid phosphates have exceeded blood phosphate.

3. *The presence in the cerebro-spinal fluid of substances which though normally present in the blood are normally absent from the cerebro-spinal fluid, e.g. fibrinogen, giving the characteristic 'feathery' clot of tuberculous meningitis.*

4. *The passage into the cerebro-spinal fluid of foreign substances injected into the blood which normally do not pass the choroid plexus.* If potassium iodide is given by the mouth, per rectum, or intravenously, the resulting increase in the cerebro-spinal fluid is so small that, until Osborne (30) applied Kendall's method for estimating iodide in the cerebro-spinal fluid, no increase was detected. Catton (31), applying chemical and electrolytic tests, was unable to detect iodides in the cerebro-spinal fluid even after prolonged administration of the drug. In the meningitides, however, the administration of potassium iodide is in many cases followed by its appearance in the cerebro-spinal fluid. Milian (32) quotes many examples of the permeability of the choroid plexus to iodides not only in tuberculous, but also in acute syphilitic (33) and cerebro-spinal meningitis (34).⁴

Mestrezat's work on nitrates in the cerebro-spinal fluid affords a further example of this type. Normally cerebro-spinal fluid contains 10 mg. per litre. If the patient be given 1 grm. of NaNO_3 per 30 kg. body weight and the spine tapped three hours later, the increase found under normal conditions is not greater than 1 to 3 mg.; thus the physiological permeability is practically nil. In chronic nervous affections (tabes, arterio-sclerosis, cerebral softening, disseminate sclerosis, spinal syphilis) the rise is rarely 5-10 mg. In meningitis, however, be it tuberculous, cerebro-spinal, or acute syphilitic, a rise of 30 to 75 mg. occurs, with a mean of 60 mg. per litre.

The resistance of the normal choroid plexus to the passage of certain immune bodies is strikingly shown by Flexner, Amoss, and Eberson (35, 36). They found that agglutinins for the meningococcus were absent from the cerebro-spinal fluid of monkeys rendered actively or passively immune to this organism. The intraspinal injection of either normal horse serum or a culture of living meningococci allows these agglutinins for the meningococcus to pass from the blood to the cerebro-spinal fluid, and the rate of passage is affected by the severity of the inflammation which is induced in the meninges.

The above four groups of changes lead us to adopt the view that the *main factor influencing the chemical composition of cerebro-spinal fluid in meningitis is the degree of damage to the cells of the choroid plexus and cerebral blood-vessels (37) by the invading virus or toxin. This impairs the vitality of these cells and increases their permeability, and thus causes the cerebro-spinal fluid to approximate to the blood-plasma in chemical composition.* Also, we suggest that the slightly higher average inorganic phosphorus content of cerebro-spinal fluid in chronic nervous diseases is best explained by the same mechanism rather than by any liberation of inorganic phosphorus due to degeneration of nerve tissue.

⁴ See also my paper, *Lancet*, London, 1924, cccv. 127.

Conclusions.

The following conclusions are based on the examination of the inorganic phosphorus content of over 150 cerebro-spinal fluids by a uniform technique:

1. The inorg. P. content of normal cerebro-spinal fluid is 1.25 to 2 mg. per 100 c.c.

2. In meningitis—tuberculous, acute syphilitic, and meningococcal—a definite increase of inorg. P. occurs; in acute epidemic encephalitis (lethargica) no increase occurs. This fact is of diagnostic importance.

3. In chronic nervous disease the cerebro-spinal fluid shows a very slightly higher average inorg. P. content than normal—0.18 mg. per 100 c.c.

4. There is no evidence that lipid break-down affects the phosphate content of the cerebro-spinal fluid during life; after death it appears to be a factor of great importance.

5. Evidence is brought forward to show that the increase found in meningitis is due to increased permeability of the cells of the choroid plexus (possibly other cerebral vessels); it is probable also that this factor accounts for the slightly higher average in chronic nervous disease.

6. There is strong evidence that the inorg. P. content of cerebro-spinal fluid is independent of—

- (1) Blood-plasma content of inorg. P.
- (2) Age of patient.
- (3) Proximity of death.
- (4) Cell or protein content of fluid.
- (5) Previous lumbar punctures.
- (6) Bacterial activity.

7. A general law embracing the chemical changes in cerebro-spinal fluid from meningitis is suggested.

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THE PROTEINS OF THE SERUM IN CANCER

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Introduction.

In a series of papers Loeper and his fellow-workers have drawn attention to an alteration in the proteins of the serum in cases of cancer. They describe an increase in the total protein which is found to be due to an increase in the amount of globulin only; the 'sérine' (serum albumin) is always diminished. In one of their papers (1) they give the following figures in illustration of these statements:

TABLE I.

	Sérum normal. p. 100.	Sérum cancer du foie. p. 100.	Sérum cancer gastrique. p. 100.	Sérum cancer du sein. p. 100.
Sérine	63	25	49	42
Globuline	36	75	51	58
Albumine totale pour 1000 parties de sérum	82	88	75	86

One notes that the authors do not state the number of instances upon which the figures given under 'sérum normal' are based, nor do they describe the range of the variations which presumably occur among normal persons. However, in a paper published a fortnight previously (2) they give the range of variation of the normal total protein as from 78 to 80 gm. per 1,000, which, by the way, would exclude the normal amount of 82 gm. which appears in the table above; while in a third paper (3) one reads that 'Le taux des albumines sériques dépasse rarement 75 pour 1000 parties de sérum'.

In the second of these papers (2) they give figures for the 'albumine totale' only in the serum in eighteen cases of cancer; these results may be summarized as follows:

	Grm. per 1,000.
More than normal amount (8 cases)	86.5, 86.0, 89.18, 83.0, 81.25, 87.5, 92.0, 80.5
Normal amount or less (10 cases)	68.8, 73.25, 62.1, 73.5, 73.9, 74.3, 65.0, 71.0, 76.5, 74.6

There is thus an increase over the normal amount, stated in this paper to be 78 to 80 gm. per 1,000, in eight (the authors say nine) cases out of eighteen; the amounts of globulin are not stated.

The authors find that the increase in serum protein occurs even in cachectic individuals, and in the absence of 'déshydratation'; the diminution in serum albumin is held to be a function of the cachexia. The additional amount of globulin is thought to come from the tumour for the following reasons:

1. Anaphylactic tests (6). The proteins were prepared by precipitation with alcohol, (a) from various carcinomata, and (b) from the sera of cancer patients; with these proteins anaphylactic tests were made on guinea-pigs. The results may be summarized as follows:

TABLE II.

Experiment.	Source of protein.		Anaphylactic shock.	
	First dose.	Second dose.		
1.	<i>Serum</i> , 'cancer gastrique'	Gastric cancer	+	(fatal)
2.	<i>Serum</i> , 'cancer cardia'	Gastric cancer	+	(transient)
3.	<i>Serum</i> , 'cancer estomac'	Tumour of breast	0	
4.	<i>Serum</i> , cancer of breast	Cancer of breast	0	
5.	<i>Serum</i> , normal	Cancer of breast	0	
6.	'Tumeur estomac'	<i>Serum</i> , cancer of breast	0	
7.	Tumour of breast	<i>Serum</i> , 'cancer estomac'	0	
8.	Cancer of breast	<i>Serum</i> , cancer of breast	+	(fatal)
9.	Cancer of breast	<i>Serum</i> , normal	0	

These results are in accordance with the view that proteins pass from the tumour into the circulation, with the exception that a positive result would have been expected from Experiment 4.

2. In one or perhaps two cases the protein of the serum was found to diminish after removal of the tumour. In a case of cancer of the breast the total protein fell from 88 to 76 grm per 1,000 during the month following amputation. The authors speak also of a case in which there were 44 grm. globulin to 32 grm. sérine (i. e. 57.9 per cent. globulin) one month after removal of a cancer of the breast; whether all these statements refer to one and the same patient is not clear. Such cases, of course, provide a crucial test of the origin of the globulin; it is unfortunate that the authors in their numerous papers do not describe these results in more detail.

3. The increase is greatest with 'tumeurs volumineuses et sécrétantes'; it scarcely appears, except when the tumour is undergoing disintegration, and is most often absent in association with dense, well-nourished epitheliomas.

4. '... Le taux des globulines des tumeurs est extrêmement élevé' (1); 100 grm. of dry cancer tissue were found to contain 18 to 20 grm. of protein, of which 66 per cent. was globulin (3).

5. The globulin of the serum of cancer patients, and in some cases the albumin as well, is increased during the days following the application of X-rays to the tumour (4, 5).

In normal serum, then, the albumin is said to constitute 65 per cent. and the globulin 35 per cent. of the protein. The globulin scarcely reaches 45 per cent. of the total in suppurations, pneumonias, and open tuberculosis; the authors (3) seem to imply that these affections produce the highest proportions of globulin found in non-cancerous states. In cancer, on the other hand, the globulin may amount to 58, 64, 75, or even 82 per cent. of the protein.

In no one of their numerous papers do Loeper and Tonnet present a complete statement of their results obtained from normal and pathological cases; certain examples only are given. The investigation described below was intended

to supplement their work by providing additional data upon two points, namely (a) the possibility of detecting an increase in the proportion of globulin in cases of cancer sufficiently early for the method to be of diagnostic value; and (b) the range of variation in the proportion of globulin which is found in normal and other non-cancerous states. The series tabulated below comprises 121 estimations upon 104 cases.

Method.

The serum was separated as soon as possible after the withdrawal of the blood; sera showing more than a trace of haemoglobin were rejected.

Total nitrogen. 0.1 or preferably 0.2 c.c. serum is placed in a test-tube (20 cm. x 2.5 cm.) with 2.5 c.c. concentrated H_2SO_4 , 4 drops saturated CuSO_4 , and roughly 0.15 gm. K_2SO_4 . The tube is placed in a paraffin bath at about 180°C . until all water has been driven off, and is then transferred to a metal bath ('compo' tubing melted in an enamelled saucepan over a Bunsen). This method was found very convenient, as all heating by hand is avoided; if the tubes are of good glass and the metal bath not too hot, cracking occurs but very rarely. It is easy to judge of the temperature of the metal bath by observing the mobility of the liquid. The Kjeldahl is completed by the method described in a previous paper (7).

Globulin nitrogen. 1 c.c. serum is placed in a tube (135 mm. x 7 mm. int. diam.) which is marked at the 5 c.c. level. A stock of MgSO_4 solution saturated at 37°C . is kept in the incubator; the tube is filled with this solution to the 5 c.c. level, corked, inverted 20 times, and placed in a warm place (at about 22°C .) overnight. Some part of the space underneath a gas-heated incubator will be found to have a suitable temperature. Next day it will almost always be found that some sulphate crystals have formed at the bottom of the tube; these show that saturation has been reached, but are not sufficiently bulky to produce any appreciable concentration of the liquid. This method of saturating is much more convenient than the process of shaking cold diluted serum with solid salt, whereby some mechanical coagulum may be produced. Possibly the precipitate is not exactly the same in composition as precipitates produced at lower room-temperatures, but for comparative purposes this is not important. The liquid is then mixed by inversion, filtered, and 1 c.c. of the filtrate combusted with 2.5 c.c. of H_2SO_4 and 4 drops saturated CuSO_4 ; owing to the large amount of salt present a little care is necessary towards the end to ensure that combustion is completed before bumping begins. No proof is offered in this paper that the whole of the nitrogenous material precipitated by MgSO_4 is actually globulin.

Non-protein nitrogen. This estimation was carried out by the method described previously (7), whenever enough serum (i. e. not less than 4 c.c. for duplicate estimations) was available.

In the numerous cases in which the amount of serum available did not admit of an estimation of non-protein nitrogen, it was necessary to regard the figure for the total nitrogen of the serum as representing the total *protein* nitrogen only. This, of course, introduces an error, the effect of which is to increase the figure given for the albumin nitrogen by the amount of non-protein nitrogen actually present, and hence to lower the figure given in the last column of the tables for the globulin as a percentage of the total protein. But from the present point of view this error is not at all serious; it lowers the figure for the globulin as a percentage of the total protein by from 0.7 to 1.5. Wherever the non-protein nitrogen was estimated the figures are given in the tables both with and without allowance for this amount, so that it is easy to judge from the tables of the error introduced. The results relating to protein are expressed in the tables

The results are given in Table III and the figure below. In the table the cases are divided into five classes according to the relative proportions of albumin and globulin in the serum; the limits of these classes are as follows:

Case.	Age.			Nitrogen mg. per cent.					
				Total.	Non-protein.	Total protein.	Albumin.	Globulin.	Globulin per cent. of total protein.
1	39	Gastric ulcer	D.	910					
					37	873	714	196	21.5
							677	196	22.5

Case.	Age.			Total.	Non-protein.	Total protein.	Albumin.	Globulin.	Globulin per cent of total protein.
2	52	Splenomegalic polycythaemia	D.	1043			731	312	30.0
3	24	Hydronephrosis	D.	941			651	290	30.8
4	43	Tuberc. cervical glands	D.	1032			698	334	32.4
5	43	Chronic appendicitis	D.	1148			766	382	33.3
6	49	Appendicitis	D.	1018			672	346	34.0
7	44	Peritoneal adhesions	D.	1032	35	983	637	346	35.2
8	32	Fistula in ano	D.	1046			680	352	34.1
9		Under anti-syphilitic treatment	D.	1140			679	367	35.1
10	40	Duodenal ulcer	D.	1260			733	407	35.7
11		Sore on vulva	D.	1158			805	455	36.1
12	40	Suppurating dental cyst	D.	1253			731	427	36.9
13	37	Cervical erosion	D.	1155			777	476	38.0
14	45	Skin eruption	D.	1190			700	455	39.4
15	50	Injury to shoulder-joint	D.	1039			716	474	39.8
		Mean		1104			625	414	39.9
16	42	Normal					712	392	
		18.viii.22		1200			768	432	36.0
		23.viii.22		1176			759	417	35.5
		29.viii.22		1146	31	1115	728	418	36.5
		2.x.22		1235			697	418	37.5
		4.xii.22		1195	27	1208	770	465	37.6
		19.i.23		1200			743	465	38.5
		11.iv.23		1211			728	467	39.1
							749	451	37.5
							738	473	39.1
C. 17	73	Early cancer due to tar	D.	1050			735	315	30.0
C. 18	39	Operable cancer of breast	D.	959			672	287	30.0
C. 19	61	Operable cancer of rectum	d.a.o.	1017			677	340	33.4
T. 20	68	Mixed parotid tumour, recurrent	D.	1116	29	988	648	340	34.4
C. 21	48	Inoperable recurrent cancer after breast amputation	H.	1088			742	374	33.5
C. 22	59	Inoperable epithelioma of nostril 17.x.22.	d.153	1118			721	367	33.7
C. 23	61	Operable cancer of rectum	D.	1106			735	383	34.3
C. 24	43	Inoperable recurrent cancer after breast amputation	H.	1085	45	1061	721	385	34.8
?	66	Cancer of rectum, 2 years after excision, no recurrence	D.	1025			676	385	36.3
C. 26	52	Inoperable cancer of rectum	D.	1022			700	385	35.5
C. 27	50	Operable cancer of breast	D.	1179			658	367	35.8
C. 28	40	Operable cancer of breast	D.	1079			642	380	36.2
C. 29	50	Operable cancer of breast	D.	952			740	439	37.2
C. 30	53	Inoperable cancer of pylorus 13.x.22	d.131	756			672	407	37.7
					25	731	591	361	37.8
C. 31	53	Inoperable cancer of cervix 21.iv.23	d.82	1046			470	286	37.8
S. 32	65	Recurrent spindle-celled sarcoma of jaw	d.149	1053			445	286	39.1
C. 33	52	Operable spheroidal-celled cancer of neck, before excision 2.x.22	d.222	1123			644	402	38.4
C. 34	61	Inoperable cancer of cervix	D.	1062			637	416	39.5
C. 35	28	Operable cancer of rectum	D.	1155			677	446	39.7
		Mean		1052			660	392	

TABLE III (continued).

Class III. Globulin 40 to 50 per cent.

Case.	Age.				Total.	Nitrogen mg. per cent.				Globulin per cent. of total protein.
						Non-protein.	Total protein.	Albumin.	Globulin.	
36		Pregnancy			882			530	352	40.0
37	57	Osteo-arthritis of hip-joint	D.		1033			621	412	40.0
						29	1004	592	412	41.0
38	29	Chronic appendicitis	D.		1163			692	471	40.5
39	32	Appendicitis	D.		1055			626	429	40.7
						40	1015	586	429	42.3
40	33	Uterine fibroid	D.		1120			658	462	41.2
41	54	Multiple non-malignant ulcers of tongue	D.		1118			647	471	42.1
42	49	Appendicitis	D.		1197			686	511	42.7
43	54	Retained pessary	D.		1139			634	505	44.3
44		Pregnancy	D.		1045			582	463	44.3
45	38	Inguinal hernia	D.		1200			661	539	44.9
46	39	? Gastritis, salpingitis	D.		871			479	392	45.0
47	33	Cystic goitre	D.		1043			549	494	47.3
48	58	Lymphadenoma	H.		969			507	462	47.7
						32	937	475	462	49.3
49	62	Enlarged prostate	D.	9.xi.22	1004			523	481	47.9
				21.xi.22	980			556	424	43.3
				Mean	1055			597	458	
T. 50	26	Endothelioma of antrum	D.		1144			686	458	40.0
C. 51	27	Inoperable hypernephroma	d.306		1144			686	458	40.0
?C. 52	64	Axillary glands, ?secondary to epithelioma	D.		1158			693	465	40.2
C. 53	42	Cancer of breast, 1 month after amputation	D.		1088			647	441	40.5
C. 54	51	Cancer of cervix, ?operable	D.		1127			668	459	40.7
						14	1113	654	459	41.2
C. 55	57	Cancer of breast, recurrence in scar	d.53		1116			661	455	40.8
						26	1090	635	455	41.8
?C. 56	73	Pigmental wart, ?malignant	D.		941			556	385	40.9
C. 57	65	Recurrent epithelioma of tongue	D.		1141			672	469	41.1
C. 58	72	Inoperable cancer of breast	H.		1029			602	427	41.5
C. 59	63	Operable cancer of breast	D.		1262			735	527	41.8
C. 60	55	Operable adenomatous cancer of scalp, ?secondary to breast	d.150		1064			616	448	42.1
C. 61	59	Inoperable cancer of bladder	d.32		945			539	406	42.1
C. 30	53	Inoperable cancer of pylorus			796			458	338	42.4
				27.ix.22						
				2.x.22	737			438	338	43.6
				7.xi.22	738			440	297	40.3
			d.106		738			413	325	44.0
C. 62	63	Operable epithelioma of tongue. Diabetes	D.		1246			717	529	42.5
C. 63	37	Operable cancer of breast	D.		994			570	424	42.6
C. 64	50	Inoperable glands secondary to epithelioma of lip	D.		1183			679	504	42.6
S. 65	33	Mixed-cell sarcoma of thigh, inoperable metastases	d.280		1057			603	454	43.0
C. 66	72	Operable cancer of rectum	d.a.o.		1113			633	480	43.1
C. 67	45	Inoperable cancer of rectum	d.279		955			535	420	44.0
				7.x.22						
C. 68	63	After removal of recurrent axillary glands, cancer of breast	D.		1155			644	511	44.3

TABLE III (*continued*).

Class V. Globulin over 55 per cent.

Case.	Age.				Nitrogen mg. per cent.					Globulin per cent. of total protein.
					Total.	Non-protein.	Total protein.	Albumin.	Globulin.	
C. 93	61	Inoperable cancer of cervix	D.	1241				557	684	55.1
C. 94	51	Inoperable epithelioma of cheek	d. 8	975				432	543	55.7
C. 87	52	Inoperable cancer of antrum	H.	1312				574	738	56.2
		5. x. 22								
						28	1284	546	738	57.5
C. 95	62	Inoperable cancer of cervix	d. 26	1027				434	593	57.7
C. 96	45	Inoperable cancer of cervix	D.	1267				521	746	58.9
C. 97	65	Inoperable rodent ulcer of face	d. 21	1097				442	655	59.7
C. 98	63	Cancer of oesophagus	D.	1127				449	678	60.2
C. 99	55	Operable cancer of tongue	d. 249	1372				525	847	61.7
C. 100	50	Inoperable cancer of neck	d. 6	997				369	628	63.0
C. 101	60	Inoperable cancer of rectum	d. 185	1146				414	732	63.9
C. 102	45	Inoperable cancer of antrum	d. 26	1449				514	935	64.5
T. 103	62	Inoperable malignant tumour of face	D.	1204				357	847	70.3
C. 104	55	Inoperable cancer of pylorus	d.a.o.	1309				324	985	75.2
						30	1279	294	985	77.0
		Mean		1194				455	739	

Discussion of Results given in Table III.

1. Class V (globulin over 55 per cent.) consists solely of cases of malignant disease, of which one was operable and twelve inoperable; the highest proportion of globulin recorded is 77.0 per cent. Yet many inoperable cases of cancer have no higher proportion of globulin than do normal persons; thus in Class II cf. the inoperable cases Nos. 26, 31, and 34, with the normal No. 16. Case 31 (carcinoma of cervix) was so advanced as to have a vesico-vaginal fistula, yet the percentage of globulin is the same as in the normal person No. 16. Evidently, then, it is quite out of the question to use any result showing a normal proportion of globulin as diagnostic evidence against the existence of cancer in any given case. On the other hand, in the advanced cases showing an abnormal proportion of globulin, the diagnosis is almost always beyond doubt from purely clinical evidence alone. In only two of the thirteen cases in Class V was the malignant nature of the disease at all doubtful, and these two were, curiously enough, those in which the percentages of globulin were the highest of all (Nos. 103 and 104). The diagnostic value of the method is therefore, at most, extremely limited. The highest proportion of globulin found in a non-cancerous case was 54.5 in case 84.

One can account for the fact that one tumour produces so much more globulin than another only by assumptions as to differences in the rate of disintegration; these cannot be put to any quantitative test, and do not assist in the solution of the question.

2. The averages given in Table IV show that no distinct increase in the total protein of the serum ('albuminose' of Loeper and Tonnet) occurs until the proportion of globulin reaches that characteristic of Class V; the average totals in the other classes are all very nearly the same, both in the cancerous and non-cancerous cases. There must then be some mechanism by which the sum of

TABLE IV.

Mean percentages of nitrogen in serum.

Globulin per cent. of total protein.		Tumours.			Other conditions.		
		Total.	Albumin.	Globulin.	Total.	Albumin.	Globulin.
Class II.	30 to 40	1052	660	392	1104	712	392
III.	40 to 50	1079	610	469	1055	597	458
IV.	50 to 55	1060	512	548	1084	511	573
V.	over 55	1194	455	739			

TABLE V.

Nitrogen mg. per cent.

Case		Date.	Total.	Albumin.	Globulin.	Globulin per cent. of total protein.
30	Inoperable cancer of pylorus	27.ix.22	796	458	338	42.4
		2.x.22	737	440	297	40.3
		13.x.22	756	470	286	37.8
		d. 106	7.xj.22	738	413	325
31	Inoperable cancer of cervix	15.ii.23	1057	574	483	45.7
		d. 82	21.iv.23	1046	644	402
33	Spheroidal-celled cancer of neck, before excision 5 months after excision ; recurrence	2.x.22	1123	677	446	39.7
		d. 90	12.iii.23	1118	588	530
22	Inoperable epithelioma of nostril	17.x.22	1118	735	383	34.3
		d. 41	5.ii.23	1050	518	532
67	Inoperable cancer of rectum	7.x.22	955	535	420	44.0
		d. 186	8.i.23	1022	507	515
87	Inoperable cancer of antrum	5.x.22	1312	574	738	56.2
		12.iii.23	1183	576	607	51.3
89	Inoperable recurrent supra-clavicular glands, cancer of breast	17.viii.22	1125	583	592	52.6
		27.ix.22	1151	574	579	50.3
92	Inoperable cancer of stomach	5.x.22	910	427	483	53.0
		13.x.22	861	397	464	53.9

albumin + globulin is kept approximately constant, the former protein being withdrawn from the blood as the latter is added to it; in Class V this mechanism, which probably serves chiefly to maintain a suitable viscosity of the blood, fails to keep pace with the liberation of globulin. The abnormally high absolute amount of globulin in Class V shows that the phenomenon studied in this paper is not simply a diminution in the proportion of albumin.

3. The data given in Table III show that in many of the cases of cancer in Classes IV and V the disease was within a few weeks of its fatal end. Yet, if it be agreed that the abnormal amounts of globulin come from the tumour, the circulation of these persons was flooded with tumour products. Hence these products did not produce any perceptible immunization; possibly they had the opposite effect. This point is of interest in connexion with the statement that the beneficial effect of X-rays in cancer is due in part to the immunizing action of the substances liberated from the damaged tumour; if this be the case, such substances must be different from those produced by the tumour spontaneously.

4. Successive observations upon the same case (Table V) have given irregular results. When the proportion of globulin rises with the passage of time, as in Cases 22, 33, and 67, this can, of course, be attributed to increasing disintegration of the tumour; but when the change is in the opposite direction, one must think of some other explanation.

5. The effect of excision of the tumour has not been observed, for no operable case has been met with in which the amount of globulin was abnormal.

6. The variations in the serum proteins which occur in a healthy person are shown by the series of observations extending over eight months upon Case 16; the proportion of globulin found ranges from 35.5 to 39.1 per cent. of the total protein.

The very few cases of sarcoma in the series have not shown any special features. Loeper and Tonnet do not deal with this class of tumour.

Summary.

Some advanced cases of cancer show an increase in the globulin of the serum which is greater than any which has been found in other conditions. There is at the same time a diminution, probably of a compensatory nature, in the serum albumin; the net effect is an increase in the total protein. It seems probable that the additional amount of globulin comes from the tumour; the clinical course of these cases shows that it has no appreciable immunizing action. This increase in globulin is very seldom perceptible sufficiently early to be of use in diagnosis. Other cases of cancer, apparently equally advanced, show no increase in the globulin.

A method is described for the estimation of serum proteins.

I wish to express my thanks to the medical and surgical staff of the Cancer Hospital for the material which forms the subject of this paper.

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A CLINICAL BLOOD COAGULOMETER

By OWEN S. GIBBS

(Department of Pharmacology, University of Edinburgh)

With Plate 19

Historical.

THE rate at which the blood clots in clinical cases is often of importance, but the measurements given are frequently of little value, because unsatisfactory methods of estimating the clotting time have been used. Several coagulometers have been described, and the principles governing their use have been laid down by Addis (1), Buckmaster (2), and Dale and Laidlaw (3); broadly speaking, two chief points must be borne in mind, a constant minimum of foreign contact and the regulation of the temperature at which observations are made. To these scientific principles one may add that for clinical purposes the amount of blood should be as small as possible, the instrument simple, and the end-point definite.

As regards the coagulometers proposed in recent years, that of Addis is so complicated as to be inapplicable to ordinary routine work. Inchley's (4) method, which is a simple modification of Buckmaster's, consists essentially of a film of blood formed in a loop; when this is held vertically, a clear space forms at the top of the film, and as long as the blood is not clotted this clear space moves when the loop is rotated, while it disappears when the clot is formed. The end-point is indefinite, and the method requires practice to get consistent results. The principle is illustrated in Plate 19, Fig. 1.

Dale and Laidlaw's apparatus is a short capillary tube with a small lead shot inside. The tube is filled with blood and held in a suitable clamp; on rotation the shot runs up and down until coagulation occurs, when it stops. The end-point is sharp, and the only drawback of the method is that each observation requires a new tube, and for a large number of observations the manufacture of a sufficient number is a serious matter, while they are expensive to buy. The amount of blood is rather large for one prick, and in some cases difficult to obtain, particularly if repeated tests are required.

Description of Method.

The method I have used, and found to be both simple and accurate, consists in forming a bead of blood on a thin wire, which on being tilted allows the bead

to run up and down, just as one of glass would ; at the moment of coagulation the bead stops and adheres to the wire. The end-point is sharp, and the method requires very little practice to obtain consistent results.

The form of the apparatus is shown in the sketch (Fig. 1).

It consists of a piece of No. 31 S.W.G. platinum wire twisted on a rod to form a loop 5 mm. in diameter (A). The wire is cut through on one side at the base of the loop (B). It is advisable to run a little silver solder into the twisted stem to about 2 mm. from the loop, as this material strengthens it. A still better plan is to silver solder a thicker piece of copper or nickel wire on to a loop with a short stem. No solder should be allowed to contaminate the loop itself. This is attached to a holder by means of a set screw S, and is protected by a very narrow brass

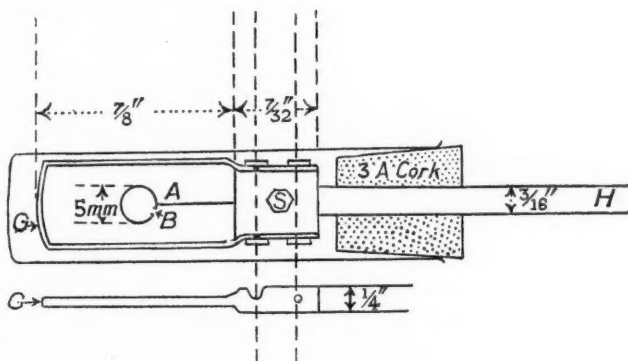


FIG. 1.

guard G which, for convenience of cleaning or replacing the loop, can be swung to one side. On the aluminium handle H, which is about 4 in. long, is a rubber cork that fits into a short glass tube. The tubes are made from ordinary test-tubes by drawing them out over a Bunsen; a small hole is left at the bottom to allow of the escape of air.

The procedure is as follows: A basin of water maintained at 37° C. is arranged in a good light. The tube is washed out in the basin and placed in a convenient position. The patient's finger is pricked and a single drop of blood obtained; at this instant a stop-watch is started, preferably by an assistant. The loop is then slipped through the drop in such a direction that the gap is the last portion of the loop to leave the blood. If this is correctly done, a film is formed in the loop which tears the moment the gap leaves the blood, forming in its place a drop, or drops, of blood on the wire. The instrument is then rapidly pushed into its tube and plunged into the basin of water. In a few seconds the drop runs freely up and down the wire when the instrument is rotated backwards and forwards. Rotation is continued until the bead stops moving, at which point the watch is stopped and the time noted. When several small drops form, gently tapping the instrument readily brings them together.

With any method variations occur in the coagulation times, and I have tried to measure and eliminate the known factors, such as the temperature, the blood, the instrument, the manipulation.

The temperature is kept constant by some form of water-bath, such as a large basin over a Bunsen burner, adjusted to keep the temperature between 35° and 40° C. Hot water may be added to the basin, as the temperature tends to fall, or other means may be employed. Between 35° and 40° C. no definite variation in the rate of clotting appears, and if 37° C. be aimed at, some latitude is allowed in each direction. With a fair-sized basin it is easy to keep the temperature steady. Below 35° small alterations of temperature have more marked effects, as the end-point is delayed and sluggish.

The blood itself must be obtained under as constant conditions as is possible. The coagulation time varies with the amount of, and probably the kind of, damaged tissue the blood comes in contact with; thus the pricks should be as much alike as possible, and as an edged instrument tends to cut more unevenly than a needle, this latter is preferred. The depth should also be the same. The form of pricker I use is a 'soft tone' (thin) gramophone needle which is held in a suitable holder. Whether the first, second, or third drop of blood is taken is indifferent, provided it is obtained within twenty seconds of the prick. Usually one takes the first drop; the results are not impaired by squeezing the finger or congesting the finger for two minutes, in which time it is blue and painful. Previously heating or cooling the hand produces no variation.

In the instrument several factors require attention. The surfaces in contact with the blood must remain constant, even slight alterations producing noticeable effects. Platinum is the best material for the loop, as it is easily cleaned and not easily tarnished, and thus gives the most constant results. Different metals give different end-points, but of those tested, which included copper, iron, platinum, palladium, silver, gold, gold alloy, tungsten, nickel, brass, resistance wire, also glass and quartz, platinum was the most satisfactory.

The gas in the tube seems to have very little, if any, specific effect, CO₂ and O₂ and air giving the same results. The humidity, however, is important, dry air giving a slow end-point. The blood does not run well in very dry air; one avoids this difficulty by using wet tubes as already mentioned. There must be no trace of volatile bodies, such as ether, alcohol, or chloroform, in contact with the blood, as these seriously delay coagulation. They should therefore not be used for cleansing either the finger or the instrument.

The loop is cleansed by removing the clot with a piece of linen or cotton cloth and washing in clean water, preferably distilled as being less liable to cause deposits on the wire; it is not, however, essential. The wire is then heated white-hot in a Bunsen or spirit flame. In cleansing one may bend the loop, but provided there are no sharp bends the actual shape has been proved to have no appreciable effect. After some time the loop gets rough with use, and it should then be replaced. Failure of the blood to run well indicates a dirty or damaged loop.

Regarding the speed of manipulation, one can with a little practice get blood from a prick into a water-bath in seven seconds, but no essential difference is found if the delay is not more than twenty seconds. The amount of blood taken up varies a little, but is more or less self-limiting; if too large a drop is formed it falls off; if too small it fails to run. Between these limits the size of the drop has no demonstrable relation to the coagulation time. The weight of a good drop is 1.5 mg.

The rate of rotation should be 70-80 per minute, but between 40 and 150 no great difference appears, the fast turning giving a slightly delayed end-point.

In order to get consistent results, it is extremely important to obtain the blood from separate pricks for each observation and preferably from separate fingers also. Below are two sets of results chosen at random and obtained without any special precautions.

1.	2.
secs.	secs.
107	106
102	84
90	94
100	112
78	100
87	96
	96
Average = 94	101
	96
	Average = 98

The first column contains a very low reading of 78 seconds; this result is to be regarded as exceptionally low, and was almost certainly due to a dirty loop, or to pricking too near a previous wound. A high reading can be produced by perfectly dry tubes, and these should be avoided, as already mentioned. If, however, the average of several observations be taken (six is recommended), the results are quite close, as is shown by a series of averages taken on myself between December 9 and February 10.

secs.	secs.	secs.
(1) 99	(7) 97	(12) 93
(2) 103	(8) 98	(13) 98
(3) 99	(9) 99	(14) 92
(4) 101	(10) 96	(15) 92
(5) 100	(11) 96	(16) 95
(6) 103		

Total average = 97 secs.

The cause of the variations is obscure. They also occur if one takes two loopfuls from the same drop, e. g. :

secs.	secs.
(1) 96	99
(2) 101	92
(3) 96	102
(4) 117	105

This variation also occurs with Dale and Laidlaw's method, and markedly so with Inchley's. All the previous results are obtained with single drops of

blood from separate fingers, following the usual lines of procedure. One of the chief factors of variation is undoubtedly the amount of contact with, and possibly the kind of, damaged tissue, which, in normal persons and animals, always tends to shorten the coagulation time. This fact is readily demonstrated if, instead of making a fresh wound for each observation, successive drops of blood are taken from the same wound; four to six drops are easily obtained, and, with practice, as many as twelve can be secured. In this way a series of observations are made which, when plotted, give such curves as are shown below.

The time taken between each observation depends on the clotting time of the previous drop; usually it takes 20–30 seconds to commence a fresh observation. Thus the time between the first and second drop is about two minutes, and between the others one minute.

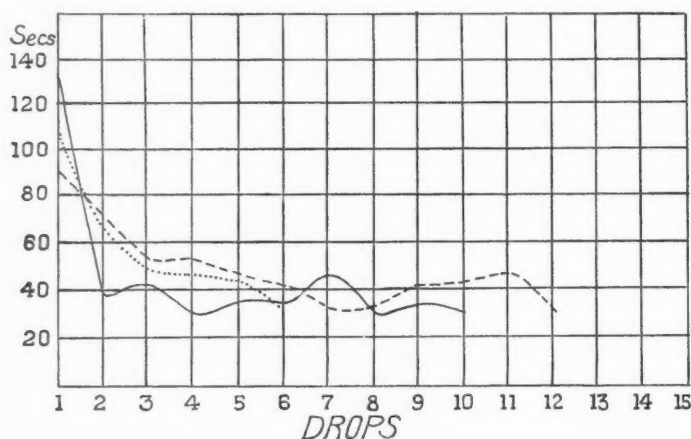


FIG. 2.

It should be noted that the shape of the curve varies somewhat, depending on the number of drops produced, which, in their turn, depend on the depth and position of the puncture. The pricks should be fairly deep and are painful (e.g. the needle should be set to a depth of 2.5 mm.–3 mm.). They are best situated about 7 mm. from the nail base and to one side of the middle line. The middle or ring fingers are the most suitable. If the prick is made too near the nail, only a few drops can usually be obtained before bleeding ceases. In the case of a big prick where mechanical stoppage is not marked, the curve is more prolonged and usually somewhat irregular at the end. The shape is, however, quite typical—a high initial point followed by a sudden drop and then a slower fall, and finally cessation of bleeding when the coagulation time is about thirty seconds. It should be emphasized that these curves require considerably more practice and skill than the taking of a single observation, which requires very little, and that a supposed variation must be confirmed a number of times before it is taken to mean anything further than an experimental error.

This local acceleration of clotting in the neighbourhood of a wound has long

been recognized, though few definite observations have been made concerning the actual times involved, efforts being more concentrated on obtaining blood with minimum of contact with damaged tissues. Clinically, however, one desires to measure the haemorrhage-arresting power of the body, which is the blood-tissue relationship, rather than the clotting of the blood itself obtained under arbitrary conditions. Probably any gross change in the blood-tissue relationship would produce a corresponding change in the end-point of blood obtained from pricks, but this cannot always be taken for granted, and therefore, since it is equally simple to measure the blood-tissue relation, it seems better to do so directly rather than trust to the indirect observation.

This method is especially suitable for clinical investigation of the action of drugs on the coagulation time. These may either affect the initial point, the shape of the blood-curve, or most probably both together. I have used it to investigate the action of calcium chloride taken intravenously by myself (e. g. 20 c.c. of a 1 per cent. solution = 0.2 gm.), which, however, gives completely negative results, there being no shortening of the initial point nor any alteration in the shape or length of the blood-curve from the normal. As an example of gross change in the blood-tissue relationship, that in a case of haemophilia is given in Fig. 3.

In this curve one finds not only an initial delay as compared with the normal, but also that the curve, although at first falling along the lines of a normal, returns not only to the initial point, but beyond it, and in this case one could obtain blood from the prick hours after. This definitely shows some serious alteration of the blood-tissue relationship, rather than any fault in the blood itself; this view was supported by the fact that addition of fresh tissue-juice or serum from a normal animal to the haemophilic blood in a test-tube caused the blood to clot practically at the same rate as a control done with blood from a normal person.

This test was made in short paraffined test-tubes kept in a water-bath at 37° C. 1 c.c. of blood was placed in each tube, to which had been previously added varying quantities of tissue-juice extract, horse-serum, &c. Blood from a normal person was also treated under exactly the same conditions. The end-point taken was when the test-tubes could be turned upside down without any displacement of the contents.

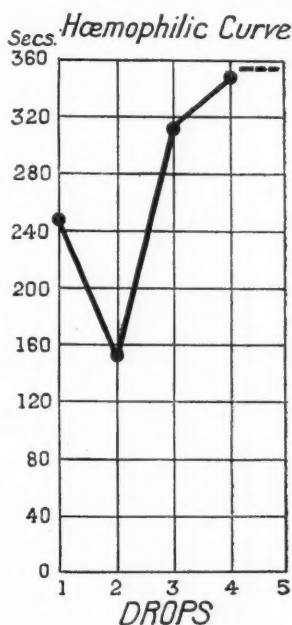


FIG. 3.

	Normal.	1 c.c. + $\frac{1}{4}$ c.c. Horse-serum.	1 c.c. + $\frac{1}{4}$ c.c. Saline.	1 c.c. + $\frac{1}{4}$ c.c. Saline Tissue Extract.
Haemophilic blood	No coag. after 1 hour	No coag. after 1 hour	No coag. after 1 hour	7 min. 14 sec.
Normal blood	5 min.	5 min. 28 sec.	13 min. 27 sec.	5 min. 10 sec.

It may be noted that this effect is only produced by fresh extracts or sera, the former losing over 50 per cent. of their power after being kept in ice for twenty-four hours. Commercial horse-serum produced very little change.

The instrument described above is not satisfactory for animal work, as it is not possible to form a film in the way described; to overcome this difficulty an instrument was designed to pick up a loopful directly, the film being afterwards torn by separating the legs of the loop. One can also use this in the same way as Inchley's instrument. In human work it has no advantage over the other simpler instrument. The hole in the cover-tube should be omitted for this type. Animal work was not continued owing to the results obtained being most unreliable in a series of observations on the same animal.

Summary.

1. A new type of blood coagulometer is described, which is simple and accurate and particularly suitable for clinical investigation.
2. Emphasis is laid on the importance of coagulation curves obtained by measuring the rate of clotting in a series of drops of blood taken from the same wound.

Part of the expense of this work was defrayed by the Moray Research Fund.

I should like to express my thanks to Professor Gulland for privileges granted in his ward.

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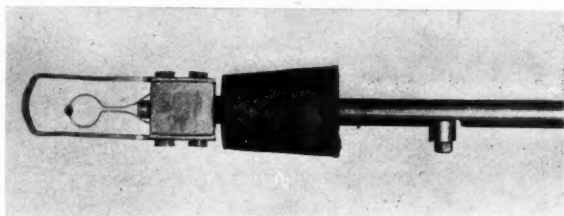


FIG. 2

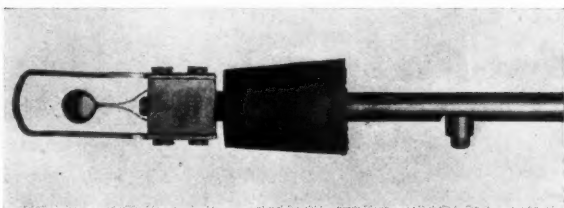


FIG. 1

ACHLORHYDRIA AND HYDROCHLORIC ACID THERAPY IN ADDISON'S (PERNICIOUS) ANAEMIA

By MAURICE E. SHAW

THE investigations here recorded were undertaken during the years 1922 and 1923 in the wards of the Medico-Neurological Clinic at Guy's Hospital under the direction of Dr. A. F. Hurst, and they formed part of a thesis submitted for the degree of Doctor of Medicine at the University of Oxford.

It appears to be sufficiently established that achlorhydria, by which is meant complete absence of free hydrochloric acid from the gastric juice, is a constant feature of Addison's anaemia. But, as far as the writer is aware, no attempt has been made to determine how large a dose of acid must be administered to remedy the deficiency, whether this dose is constant for all patients, and, if it is not constant, whether we can ascertain in a given case, by examination of the gastric juice, the dose required.

The investigations, undertaken with a view to elucidating these points, fall naturally into three parts. The first deals with the achlorhydria itself, the second with the effects of the administration of hydrochloric acid, and the third with the practical problem of the treatment of achlorhydria based upon the experimental knowledge thus gained.

I. *The Achlorhydria of Addison's Anaemia.*

Bennett and Ryle (1) have shown, by the fractional method of gastric analysis, the variations which exist in the free acid content of the gastric juice of normal individuals. Following their technique an attempt has here been made to show the variations which exist in the achlorhydria of patients suffering from Addison's anaemia. For this achlorhydria, which is recognized by the fact that the dimethyl indicator does not change colour when added to the specimens collected from a fractional test-meal, is not constant. Further, it will be found that these specimens do not give the acid reaction with litmus or Congo red. To measure this achlorhydria it is necessary to add N/10 HCl to each specimen of a fractional test-meal until the acid point is just reached. For example, if 1 c.c. of N/10 HCl is required to produce a change in a few drops of dimethyl indicator added to 5 c.c. of a specimen of gastric juice, then we can say that 100 c.c. of gastric juice have an alkalinity (or an achlorhydria)

equivalent to 20 c.c. of N/10 NaOH (= 0.08 gm. NaOH). If consecutive specimens are titrated in this way, a curve is obtained which is comparable with the free acid curve of an ordinary test-meal. Seven cases of Addison's anaemia have been investigated in this way, and the resulting curves are shown in Fig. 1. The number of cases is perhaps too small to permit of any very positive generalizations, but it will be at once obvious to those familiar with Bennett and Ryle's work that the curves shown in Fig. 1 bear a distinct resemblance in shape to the normal free acid curves found by these workers. The initial descent of each curve, corresponding to the $\frac{1}{4}$ hour immediately after the meal, is striking; thereafter the variations are comparatively small, being equivalent to from 10 to 30 c.c. N/10 NaOH per 100 c.c. of gastric contents. In other words, if the volume of the gastric contents was constant at 100 c.c., we should have to add at least 25 c.c. of N/10 HCl to correct the deficiency of acid. But naturally this volume is variable, being at its maximum immediately after a meal and thereafter diminishing. As a basis for a theoretical calculation of the quantity of acid required, we might assume 100 c.c. to be the average content over a period of two hours to two hours and a half. On this assumption 25 c.c. of N/10 HCl would be required at any given moment to bring the acidity up to a figure approaching the normal figure for free acid. This 25 c.c. would contain rather less than 0.1 gm. (0.091 gm.) of pure HCl. The B.P. preparation *Acidum hydrochloricum dilutum* contains 10 per cent. by weight of HCl, so that 0.1 gm. would be contained in 1 c.c. If such a dose were given every $\frac{1}{4}$ hour after a meal for $2\frac{1}{4}$ hours, corresponding to one dose for each specimen withdrawn, 8 c.c. of the B.P. preparation would be required. Actually, on account of the cumulative action of repeated doses, less would probably be sufficient; but, as low figures have purposely been taken, we might expect to find that the right dose of acid in an average case of Addison's anaemia would be about 8 c.c. (or ʒij) of the *Acid. hydrochlor. dil.* (B.P.).

At the same time as the above investigations were being carried out, the writer was attempting, quite apart from the theoretical considerations set out above, to determine experimentally the quantity of acid which, when orally administered, would give an approximately normal free acid curve in a case of Addison's anaemia. These researches comprise the second part of the present investigation.

II. *The Effects of administering Hydrochloric Acid in Addison's Anaemia.*

Five cases of Addison's anaemia were investigated, of whom three had already been used for the experiments recorded in the previous section. The fractional test-meal technique described by Bennett and Ryle has been used throughout. In the charts that follow, the shaded area represents the limits of free HCl in 80 per cent. of normal people (Bennett and Ryle). The dotted line represents free HCl, and the continuous line combined acid. The interrupted lines in three of the figures are the curves of these cases from Fig. 1 superimposed.

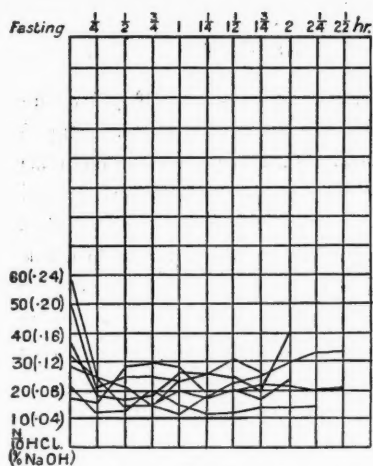


FIG. 1.

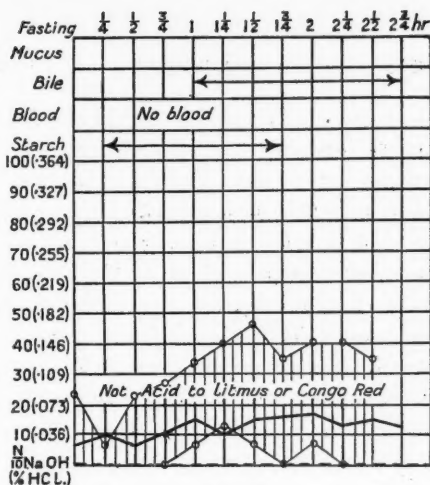


FIG. 2.

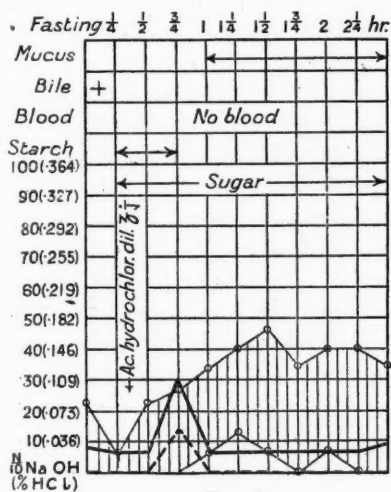


FIG. 3.

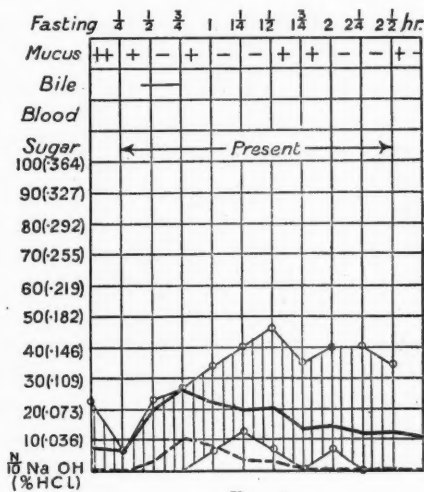


FIG. 4.

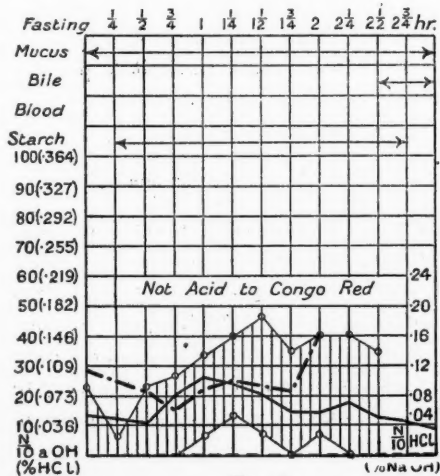


FIG. 5.

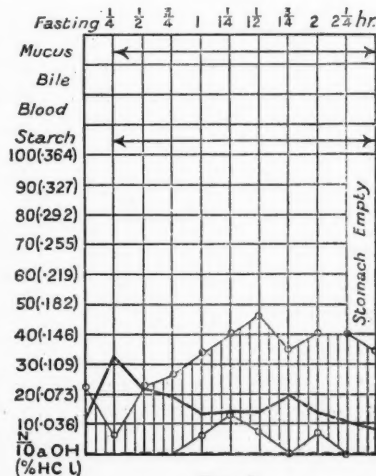


FIG. 6.

Figs. 2, 3, and 4 illustrate the first experiment undertaken. Fig. 2 is the chart from the routine test-meal, and shows complete achlorhydria. Fig. 3 shows the effect of $\bar{z}j$ of the Acid. hydrochlor. dil. B.P. administered in one dose half an hour after the meal. On account of the very transient effect of this, and with a view to reproducing more accurately the mechanism of gastric secretion, another attempt was made. The same dose was made up into a palatable drink with lemon juice, sugar, and water (about $\bar{z}vj$ in all) and the patient was instructed to sip this at intervals for an hour, commencing immediately after the meal. The result is shown in Fig. 4, and, although a comparatively low free acid curve was obtained, it is an approximate approach to a normal condition.

In order to ascertain the effects of giving the acid actually with the meal, another patient was selected. Figs. 5 and 6 show the results of a test-meal with and without acid respectively. The dose was $\bar{z}j$ (in all these experiments the pharmacopoeial preparation above referred to was used). This was clearly useless, so another attempt was made. This time the patient took $\bar{z}ij$ by the 'continuous' method as described for the previous patient. The result was startling, and not a little alarming (Fig. 7). Next, the same procedure was repeated, but the dose was halved ($\bar{z}j$)—i.e. the same dose that had produced encouraging results in the last patient. No free acid was found in any of the specimens (Fig. 8). Clearly, the right dose lay somewhere between $\bar{z}j$ and $\bar{z}ij$. The experiment was repeated with $\bar{z}jss.$ and a good curve obtained (Fig. 9).

Figs. 10 and 11 were kindly sent to me by my friend Dr. Alan Mckenzie from a case under his care at Whiston Infirmary. They show the results of $\bar{z}ij$ given by the 'continuous' method. Fig. 12 came from a case who was given $\bar{z}jss.$ by the same method. In this and subsequent charts I have suppressed the routine test-meal charts in order to save space; they all show complete absence of free acid. Fig. 13 shows the result of giving only $\bar{z}j$, and the difference between these two last charts clearly shows that while $\bar{z}j$ may be a sufficient dose, $\bar{z}jss.$ may be too small. Fig. 14 illustrates another $\bar{z}jss.$ dose, which was more successful. Finally in Fig. 15 is shown the complete absence of any free acid even after a $\bar{z}ij$ dose.

The foregoing facts appear to show that $\bar{z}j$ of acid by the continuous method is a minimum effective dose, and even so rarely sufficient, while it is possible that $\bar{z}ij$ may not be enough to produce any effect.

III. *The Treatment of Achlorhydria in Addison's Anaemia.*

The theoretical considerations discussed above at the conclusion of the first section indicated that a dose of $\bar{z}ij$ of acid was likely to be approximately correct. The experimental evidence demonstrates that $\bar{z}jss.$ to $\bar{z}ij$ or more are the limits within which effective results are obtained. Theory and practice are, therefore, sufficiently in agreement to permit it to be stated that far larger doses than have been customary in the past ought to be administered. But it is necessary to consider what is the aim and object of replacing the gastric acid in cases of

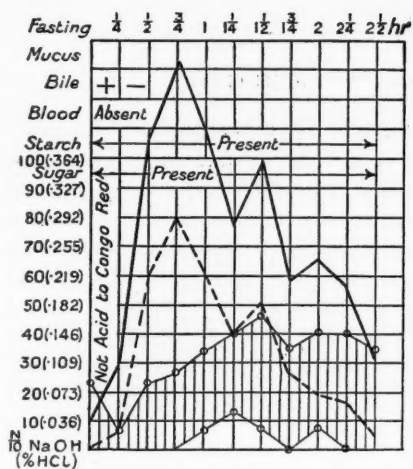


Fig. 7.

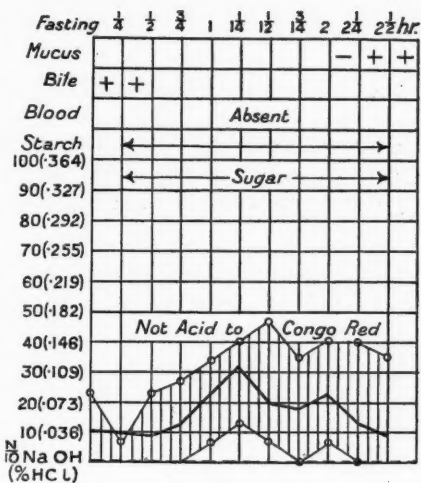


Fig. 8.

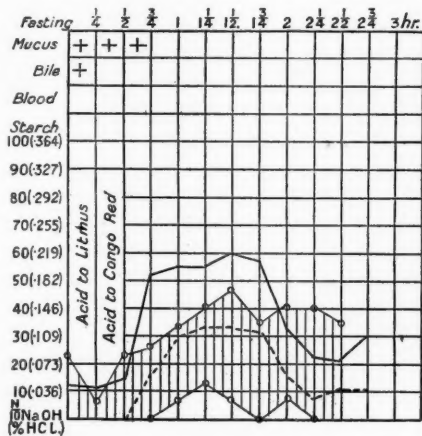


Fig. 9.

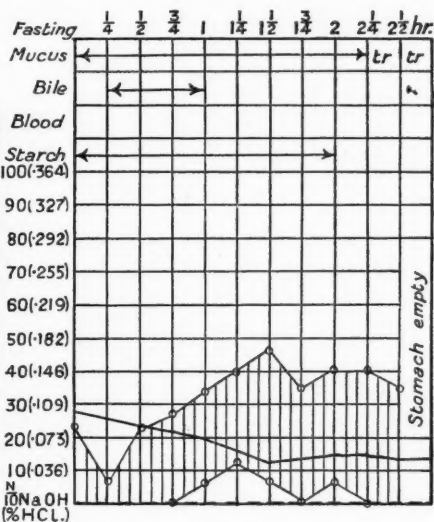


Fig. 10.

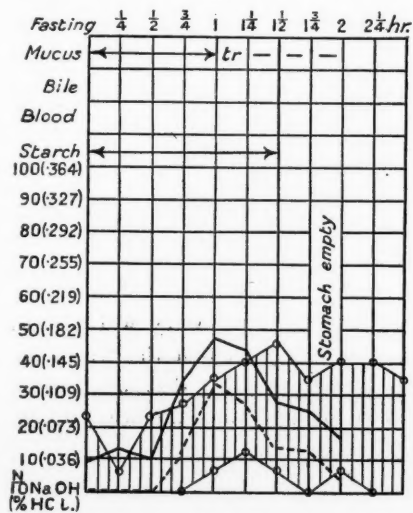


Fig. 11.

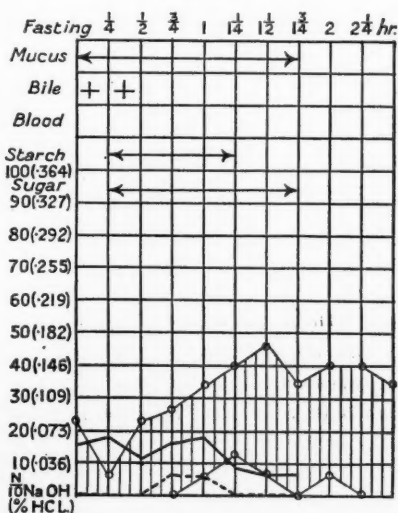


Fig. 12.

Addison's anaemia. Hurst has argued (2) that the achlorhydria of Addison's anaemia is the primary defect, and that it permits the passage of organisms, probably streptococci, into the intestinal tract, where the toxins of the disease

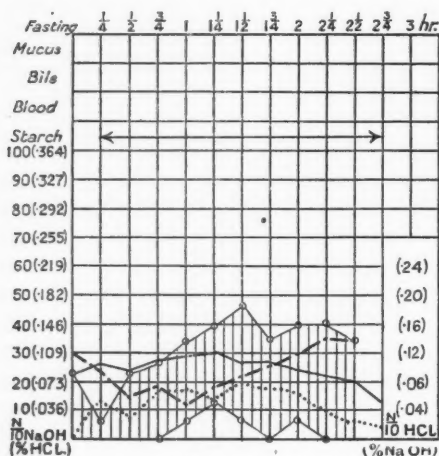


FIG. 13.

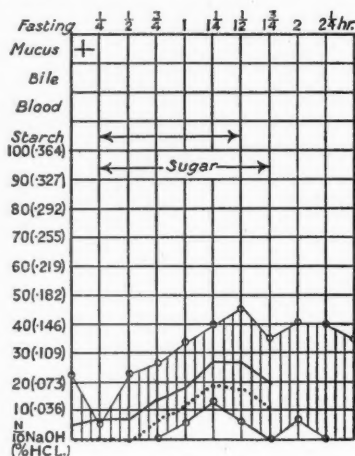


FIG. 14.

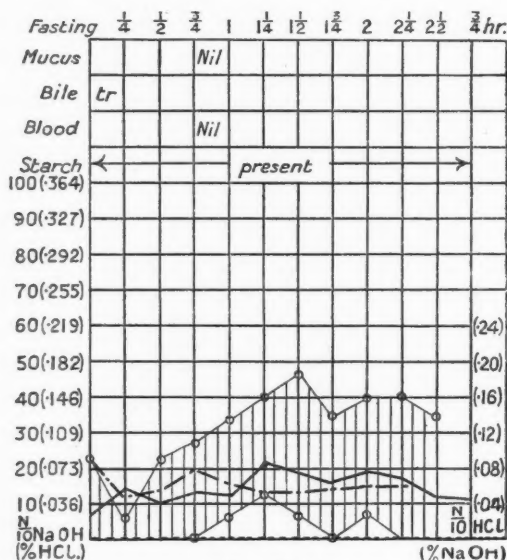


FIG. 15.

are formed and absorbed. Without entering into the controversy which rages round the aetiology of Addison's anaemia, one may yet admit the feasibility of this explanation, and one cannot be blind to the possibility that such a chain of events may enter into the aetiology of other diseases which are accompanied

by achlorhydria. The object of treatment, therefore, must be to restore the lost germicidal power of the gastric juice.

In a recent paper Knott (3) has shown that gastric juice containing 0.03 per cent. free HCl is effective in killing streptococci in twenty minutes. 0.05 per cent. is even more effective, destroying most of the organisms commonly found in gastric and duodenal contents. Clearly then the therapeutic aim should be to obtain a gastric content containing at least 0.05 per cent. free HCl for a period of time longer than twenty minutes. In the experiments recorded there were only two failures to produce such a result (Figs. 12 and 15).

Unfortunately there does not appear to be any very definite relationship between the 'alkalinity' curves shown in Fig. 1 and the amount of acid experimentally required. Both sets of experiments were performed upon three of the cases (Figs. 5, 13, and 15). Of these the lowest 'alkalinity' curve (Fig. 15) appeared in the case in which the greatest quantity of acid (3ij) produced no effect. The other two alkalinity curves are very similar (Figs. 5 and 13), and in each case 3jss. of acid were sufficient. The only certain method of determining the correct dose is the experimental method. Where this is impossible, 3jss. should be given in the way indicated.

Conclusions.

1. The achlorhydria of Addison's anaemia is absolute and can be measured. Theoretical considerations based upon the estimation of the degree of achlorhydria suggest that about 3ij of Acid. hydrochlor. dil. (B.P.) would remedy the defect.

2. Experimental evidence shows that 3jss. to 3ijss. will restore the effective germicidal activity of the gastric juice in Addison's anaemia if given by the 'continuous' method.

It is a pleasure to acknowledge my indebtedness to Dr. Hurst, at whose instigation this work was undertaken, and whose assistance in supplying me with material and much valuable advice has been unfailing; to Dr. Ryffel, who kindly placed his laboratory at my disposal; and to Sir A. Garrod, Regius Professor of Medicine in the University of Oxford, for permitting me to publish matter which has already been incorporated in a thesis submitted to that University.

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AURICULAR FIBRILLATION IN THYRO-TOXIC CONDITIONS

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With Plate 20

Introduction.

THE importance of changes in the cardio-vascular system and the occurrence of cardiac irregularities in exophthalmic goitre were recognized by the earliest writers, but it is only recently that the association of auricular fibrillation with thyro-toxic conditions has been emphasized. This is natural, in view of the comparatively recent knowledge on the differentiation of the cardiac irregularities through the development of instrumental methods of analysis.

In 1909 one of us (T. P. Dunhill) (1), in recording the results of partial thyroidectomy in hyperthyroid conditions, noted that cases with rapid and markedly irregular action of the heart before operation may, after operation, show a regular action and greatly improved circulation. The evidence was not sufficient to account for the irregularity by the presence of auricular fibrillation, but this was suspected as being the cause in some of the cases. Fahrenkamp (2), in 1914, records that four out of 120 cases of auricular fibrillation were associated with exophthalmic goitre, and that in one of the four the auricular fibrillation was transient. In 1918 Krumbhaar (3) records three cases of thyro-toxic auricular fibrillation, and one of auricular flutter, and notes that in one of them the auricular fibrillation persisted for eighteen months and disappeared coincidentally with the improvement in the general thyro-toxic manifestations. In an analysis of sixteen cases of auricular flutter in 1918, Blackford and Williams (4) note that three of them were associated with thyro-toxic states and that auricular fibrillation was produced in them by treatment with digitalis, and that after thyroidectomy the normal rhythm was restored. In the same year White and Aub (5) found six cases of auricular fibrillation out of forty-seven thyro-toxic subjects showing cardiac arrhythmias. In 1922 Howard (6), discussing the myocardial changes in exophthalmic goitre, states that 'auricular fibrillation is a common accompaniment of this myocardial degeneration'. In the same year Hamilton (7) records seven cases of established auricular fibrillation in exophthalmic goitre, in which operations were performed on the thyroid gland, and in three of them normal rhythm

was restored, while in four the auricular fibrillation persisted. In two of the four there was evidence of rheumatic disease of the heart in addition. Hamilton also records six cases of paroxysmal auricular fibrillation, and in each instance a stable normal rhythm resulted after operative treatment. The author expressed the opinion that treatment with digitalis helps in restoring the mechanism to normal. Kerr and Hensel (8) in 1923, in an analysis of thyro-toxic cases, note that out of 123 cases of toxic adenoma, auricular fibrillation was found in nine, in four of which it was paroxysmal in type, and in two others the auricular fibrillation alternated with auricular flutter, and that out of fifty-eight cases of exophthalmic goitre auricular fibrillation was present in twenty, in eleven of which it was paroxysmal in type, and in six others the auricular fibrillation alternated with auricular flutter. These authors discuss the results of treatment on the thyro-toxic condition and on the general circulatory disturbance, but do not discuss the results of the treatment on the auricular fibrillation.

The observations to be reported in this paper were made on fifteen cases of thyro-toxic auricular fibrillation that we have had opportunities of studying closely. Many other cases have been met with incidentally, especially previous to the commencement of this study. In three (Cases Nos. 1, 8, 9) of the fifteen cases no electro-cardiographic proofs of the presence of auricular fibrillation were obtained, but the clinical observations had been sufficiently close to justify their inclusion. No cases that presented evidence of valvular heart disease have been included in this series. The cases may be divided into those showing (I) Transient auricular fibrillation, of which there were four, and (II) Persistent auricular fibrillation, of which there were eleven. In some of them partial thyroidectomy was performed, and in some quinidine was administered. The study of the onset of auricular fibrillation in relation to thyro-toxic symptoms, and of the conversion to stable sinus rhythm as the result of thyroidectomy or of quinidine administration, appears to us to point to certain conclusions as to the cause of this form of auricular fibrillation and to indicate the treatment that should be adopted.

Analysis of the Observations.

I. *Transient auricular fibrillation.* In one case of severe exophthalmic goitre (Case No. 1), which has been under observation both as an out-patient and in the wards for a period of twelve months, paroxysms of auricular fibrillation, lasting a few minutes or a few hours, have been observed on five occasions. Unfortunately, no instrumental proof has been obtained, but the complete irregularity and a considerable pulse deficit allow of no doubt as to the nature of the irregularity. These paroxysms were accompanied by palpitations, and resulted in most instances from emotional disturbances, such as class demonstrations, and determinations of the basal metabolic rate. While under treatment in the ward, during which time the basal metabolic rate fell from + 70 per cent. to + 30 per cent., these paroxysms became less frequent.

In three patients with exophthalmic goitre (Cases Nos. 2, 3, and 4), an attack

of auricular fibrillation occurred immediately following the operation of partial thyroidectomy during a stage of excessive excitement and other thyro-toxic symptoms. In each case the attack ceased spontaneously, in Case No. 2 three days after the operation, in Case No. 3 eight days after, and in Case No. 4 three days after the operation, and has not recurred. The electro-cardiograms showing the rhythm during the paroxysm and after it had ceased in Case No. 3 are reproduced in Plate 20, Fig. 1.

II. *Persistent auricular fibrillation.* (1) In two cases of exophthalmic goitre and auricular fibrillation (Cases Nos. 5 and 6), no operative treatment was performed, because the thyro-toxic symptoms were of a mild type and it was considered that there was a danger of myxoedema resulting. These cases are of interest, as they illustrate the presence of auricular fibrillation at a time when the thyro-toxic symptoms are slight. This has been noted in cases of toxic adenoma by Kerr and Hensel, and we have observed it in Case No. 14, which was also one of toxic adenoma, while in Case No. 11, in which the symptoms of exophthalmic goitre were comparatively mild, the history suggests that the thyro-toxic symptoms had at one time been much more severe. It seems probable, therefore, that persistent auricular fibrillation in cases of exophthalmic goitre arising during a severely toxic stage may persist after a natural recovery has set in, and so may be found in cases showing but slight thyro-toxic symptoms and comparatively low basal metabolic rates. In the two cases under discussion (Cases Nos. 5 and 6) there is no clear history of there ever having been severe thyro-toxic symptoms, and so they may be regarded as approaching to toxic adenoma in type, although there was no clinical evidence that this was the condition of the thyroid glands.

(2) In three patients with exophthalmic goitre and persistent auricular fibrillation (Cases Nos. 7, 8, and 9), one or more operations of partial thyroidectomy were performed, and the auricular fibrillation ceased spontaneously. In Case No. 7 the abnormal rhythm had set in while under observation as an out-patient. Proof of the presence of auricular fibrillation was obtained three weeks before partial thyroidectomy was performed. Three weeks later, when a further thyroidectomy was carried out, the auricular fibrillation was still present. Twelve weeks after the second operation sinus rhythm had returned, and has persisted now for three years, without any further treatment. In Cases Nos. 8 and 9 no instrumental proof of the altered rhythm was obtained, but in Case No. 8 the heart was noted by competent medical men to be completely irregular for one month before the first partial thyroidectomy was performed. It was still quite irregular two months later when a further thyroidectomy was performed. Ten weeks later the heart was found to be regular, the patient was walking about without discomfort, and her efficiency was rapidly increasing. In Case No. 9 auricular fibrillation was known to be present for six years before the operation of partial thyroidectomy was performed. At that time heart failure was so severe that the operation was delayed for four weeks until the patient's condition became more satisfactory. Twelve days after the operation the heart became regular, and nine months later

her doctor reported that she was walking and climbing stairs with little inconvenience, and that her pulse was regular, and varied in rate from 72 to 84 per minute.

These cases show that the improvement in the thyro-toxic state, as the result of partial thyroidectomy, may bring about a return to normal rhythm, and that this return may occur at least three months after the operative treatment. The return in the two cases in which it was delayed was accompanied by a striking increase in the efficiency of the patients, who while the abnormal rhythm persists may be in constant danger of heart failure, in spite of the recovery from the initial condition of exophthalmic goitre.

(3) In four patients (Cases Nos. 10, 11, 12, and 13) with exophthalmic goitre and auricular fibrillation, partial thyroidectomy was performed, and the conversion to sinus rhythm was then brought about by the administration of quinidine sulphate. In Case No. 10 the patient stated that he had had auricular fibrillation for at least five years. A partial thyroidectomy had been performed three years previously to his coming under our observation, but he had been confined to bed off and on throughout that period with symptoms of heart failure. The thyro-toxic symptoms were still pronounced, and a further partial thyroidectomy was performed. In view of his long history it was decided to restore normal rhythm as soon as possible, and so three weeks after the operation he was given quinidine sulphate. Twenty grains, in four doses of 5 grains, at six-hour intervals, were sufficient to restore sinus rhythm, and the dose was then reduced, and the administration stopped ten days later. The normal rhythm has persisted since, and now, eight months since the conversion, he is still slowly increasing his activities and his efficiency.

Case No. 11 is similar. He stated that he had had auricular fibrillation for eight years, and had been confined to bed for long periods of time with symptoms of heart failure, in spite of treatment with digitalis. Partial thyroidectomy was performed in two stages, and three weeks later quinidine sulphate was commenced. After 250 grains the conversion to sinus rhythm occurred, and the administration was continued for ten weeks in diminishing doses, as the patient was difficult to control in regard to his activities, and the sinus rhythm was interrupted by ventricular extra-systoles. He fibrillated on one occasion for a few hours, a week after the return of sinus rhythm, during a period of intense emotional excitement, but in the five months since the conversion he has rapidly recovered his efficiency.

Case No. 12 was of special interest in that it was possible to observe the action of quinidine before operative treatment as well as after. The patient was a woman who had had exophthalmic goitre for seven years, and auricular fibrillation for several years at least. On medical treatment the thyro-toxic symptoms had subsided considerably, but heart failure with oedema had persisted. The symptoms of heart failure responded well to digitalis, and quinidine restored the sinus rhythm in two days after 30 grains had been administered. It was continued in diminishing doses for four weeks, as extra-systoles and abnormal auricular

complexes were noted. The sinus rhythm persisted for a further two months, when a severe attack of pharyngitis was accompanied by a return of auricular fibrillation and an increase in the thyro-toxic symptoms. Quinidine again restored sinus rhythm, but it was not stable, and so the drug was stopped and a partial thyroidectomy performed. Quinidine now gave a more stable sinus rhythm, and was continued for two months in diminishing doses. Her activities increased rapidly, and she felt better and stronger than she had done for many years. After four months of sinus rhythm there was another return of auricular fibrillation following heavy physical exertion, but quinidine restored the sinus rhythm promptly. It is possible that a further partial thyroidectomy will be necessary in this case to obtain stability, but, in spite of a considerable degree of exophthalmos, the general thyro-toxic symptoms are now so slight that further removal of the thyroid gland might be followed by myxoedema.

Case No. 13 was that of a female patient who had had exophthalmic goitre for three years, and auricular fibrillation for at least six months. Partial thyroidectomy was performed in two stages, with an interval of four months, and as auricular fibrillation was still present three months later quinidine was given. This case was peculiar in that the ventricular rate had become slow without any digitalis treatment, varying from 50 to 60 a minute, and coupling was present at times. Conversion to sinus rhythm resulted after 55 grains, but as the patient complained of feeling faint three days later, the administration was stopped. After a further two days, sudden death occurred. It seems probable that a ventricular standstill occurred, and that the evidence of some degree of auriculo-ventricular block should have been regarded as a contra-indication to the use of quinidine.

(4) In two patients, one with toxic adenoma (Case No. 14) and the other with exophthalmic goitre (Case No. 15), quinidine was used without any operative treatment.

In Case No. 14 a large multiple adenomatous goitre had been present for as long as the patient could remember, and auricular fibrillation with heart failure had been present for ten weeks at least. The mouth showed a severe septic condition of the gums and tooth sockets, and the tonsils showed chronic sepsis. The general thyro-toxic symptoms were not severe, and quinidine restored sinus rhythm after two days, but although the administration was continued, the rhythm was interrupted by numerous ventricular extra-systoles, by short runs of ventricular tachycardia, by abnormal auricular complexes, and by transient auricular flutter. While quinidine was still being administered, auricular fibrillation returned, with the onset of an acute tonsillar abscess and a diffuse purpuric eruption. The quinidine administration was stopped and digitalis given. After the acute infection had subsided, quinidine again restored the sinus rhythm, which was more stable on this occasion, occasional extra-systoles alone interrupting it. The tonsils were removed and all her teeth extracted, without any return of auricular fibrillation. The administration of quinidine was continued for six months, and at the end of that period the patient was working as a cook and felt

better than she had done for many years. She refused to have any operation for her goitre, but the removal of the sepsis in her mouth and tonsils has resulted apparently in a lessening of the thyro-toxic condition. Electrocardiograms illustrating the auricular fibrillation, the unstable sinus rhythm, and the final sinus rhythm, are shown in Plate 20, Fig. 2.

In Case No. 15 a persistent auricular fibrillation developed while the patient was under observation and treatment for exophthalmic goitre. On clinical examination, on admission, she was found to have auricular fibrillation, but this disappeared in twenty-four hours. The ventricular rate, when normal rhythm returned, was 110-120 to the minute, but under treatment the general symptoms had subsided and the rate had fallen to 80-90. The onset of persistent auricular fibrillation coincided with a relapse after discharge from hospital, and the ventricular rate was then 144. Quinidine promptly restored the sinus rhythm, but transient returns of auricular fibrillation are frequent. When the sinus rhythm is present, the ventricular rate varies from 100 to 130, and the patient does not feel any better than when auricular fibrillation is present. It is probable that operative treatment will be necessary before a stable normal rhythm without rapid rate can result.

Discussion.

That the onset of auricular fibrillation is associated with thyro-toxic states must be accepted, in view of the occurrence of this abnormal rhythm in thyro-toxic patients, in whom none of the other accepted causes of auricular fibrillation can be ascertained. This view is strengthened by the onset in severely toxic cases while under observation, such as Cases Nos. 1, 7, and 15, and by the return to sinus rhythm after recovery from the thyro-toxic state as a result of operation, as was seen in Cases Nos. 7, 8, and 9. On the other hand, it is difficult to see why the abnormal rhythm should occur in patients showing comparatively slight evidence of thyro-toxicosis, such as Cases Nos. 5, 6, and 14. It is a fact, however, that in cases of toxic adenoma the cardio-vascular disturbances are severe compared with the other symptoms, such as exophthalmos and mental excitement, as in Case No. 14. In cases of exophthalmic goitre also, it is well known that all the toxic phenomena are not present to an equal extent, and Cases Nos. 5 and 6 must be regarded, in the light of our present knowledge, as having proportionally severe damage to the cardio-vascular system. Whether these effects are due to chemical differences in the abnormal bodies secreted by the diseased thyroid glands, or to an abnormal susceptibility of the heart in such patients to the same toxin, cannot at present be decided.

The onset immediately following operation during the stage of excessive excitement, and the return to sinus rhythm a few days later when the general disturbance had quieted, as in Cases Nos. 2, 3, and 4, is further evidence of the thyro-toxic cause, although the use of adrenalin with the local anaesthetic deprives these observations of the full value they would otherwise have as evidence in this direction.

The action of quinidine in causing a stable sinus rhythm in patients in whom the thyro-toxic condition has improved under treatment, either by partial thyroidectomy, as in Cases Nos. 10, 11, 12, and 13, or by the natural course of the condition, as in Case No. 12, or by treatment of septic conditions, as in Case No. 14, and the unstable or transient sinus rhythm in patients in active thyro-toxic conditions, as seen in Cases Nos. 12, 14, and 15, is also evidence of the thyro-toxic state causing the auricular fibrillation.

Auricular fibrillation tends to persist when once established, and this stability of the abnormal mechanism may make it necessary in some cases, even when the original thyro-toxic condition has subsided, to use quinidine to restore the sinus rhythm. If, however, the thyro-toxic condition is still present, a stable normal rhythm is not produced, and so it is necessary to treat the thyro-toxic condition before proceeding to treat the auricular fibrillation. Even if sinus rhythm is restored in active thyro-toxic patients, as in Case No. 15, there is no obvious benefit, since the cardiac insufficiency in auricular fibrillation is mainly due to the high ventricular rate induced by the abnormal auricular rhythm, and if sinus rhythm is present the ventricular rate in such patients may be not only just as high, but it is not controlled by digitalis therapy as it is when auricular fibrillation is present.

It is difficult to prove that a patient with persistent auricular fibrillation, who is no longer thyro-toxic and whose ventricular rate is controlled by digitalis, obtains an enhanced efficiency by a return to a sinus rhythm, but the evidence is strongly in this direction in Cases Nos. 7, 8, 9, 10, 11, 12, and 14, if the subjective evidence is of value. The removal of the necessity for permanent digitalis treatment is of itself worth effecting.

In the majority of the cases it has been surprising how rapidly a return in efficiency has occurred after the cessation of the thyro-toxic state and the return to sinus rhythm, but in Case No. 10 the rate of increase in the patient's activities has been disappointing. This patient's condition may be taken as evidence pointing to a severe damage to the heart muscle as a result of the long-continued toxic state.

In the type of auricular fibrillation seen in thyro-toxic patients there would appear to be, therefore, an active toxic cause for the abnormal rhythm, and this active toxic cause can be removed by treatment. This may be all that is necessary to restore the normal sinus rhythm, or quinidine may be used to effect conversion after the cause has been removed. There is at present no evidence as to how the toxic cause acts. It may be a direct action on cardiac structures, it may be an indirect one through nervous structures or through the action on other internally secreting organs.

It would seem possible that other forms of auricular fibrillation may similarly have an active cause, chemical or bacterial, and that in them the cause must be ascertained and removed before a stable normal rhythm can be restored by quinidine.

Summary.

1. Fifteen cases of thyro-toxic auricular fibrillation have been studied.
2. In four the auricular fibrillation occurred as a transient condition, and in three of them it occurred during the stage of excessive excitement following the operation of partial thyroidectomy.
3. In eleven the auricular fibrillation was persistent previous to treatment.
4. In two of the cases of persistent auricular fibrillation the abnormal rhythm was associated with but slight evidence of general thyro-toxicosis.
5. In three of the cases of persistent auricular fibrillation a return to a stable sinus rhythm occurred after partial thyroidectomy. In two of them this did not occur until three months after the operation.
6. In four of the cases of persistent auricular fibrillation a return to a stable sinus rhythm was brought about by the action of quinidine after the operation of partial thyroidectomy.
7. In one case of persistent auricular fibrillation quinidine produced a stable sinus rhythm following the improvement in the thyro-toxic condition that occurred without operative treatment. A similar result was obtained in a case that later required operative treatment, and is included in 6.
8. In one case of persistent auricular fibrillation the thyro-toxic condition has not improved under medical treatment, and the sinus rhythm that results from quinidine is transient.

Transient or unstable sinus rhythm resulted from quinidine in two cases during severe thyro-toxic activity, but stable sinus rhythm resulted in both after quinidine, when the thyro-toxic condition had improved as the result of partial thyroidectomy in one of them (included in 6), and of medical treatment in the other (7).

Conclusions.

1. Thyro-toxic auricular fibrillation is associated with an active toxic cause.
2. Removal of the cause, as by partial thyroidectomy, will result in a return to a stable sinus rhythm in a proportion of the cases.
3. Quinidine will bring about a return to a stable sinus rhythm, if the cause has been removed and the auricular fibrillation persists.

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Case Reports.

Case No. 1. E. M., female, aged 43 years, married.

History of nervousness, tremors, sweating, and exophthalmos for two years before admission. Ovariectomy six months after onset of symptoms. Had lost 20 lb. in weight in the two years. Was attending Out-patient Department for eight months without improvement.

Admitted to hospital, March 19, 1923. Excited, anxious, sweating profusely, and changing colour easily. Slight exophthalmos and lagging of eyelids. Marked tremor of hands, tongue, lips, &c. Thyroid gland showed moderate diffuse enlargement. Apex-beat in sixth space, $4\frac{1}{2}$ in. from mid-line. Pulse-rate 110-120, regular. Teeth carious. Weight 110 lb. Basal metabolic rate + 70 per cent. Paroxysms of auricular fibrillation were noted while patient was at rest in bed on March 20, March 31, April 9, June 3, July 3. Weight dropped to 92 lb. in first four weeks. Steady improvement after first four weeks. Discharged from hospital July 19, 1923. Pulse-rate 80-90, regular. Weight 120 lb. Basal metabolic rate + 26 per cent.

Case No. 2. B. P., female, aged 45 years, married.

History of exophthalmic goitre for six years with several improvements and relapses. Oedema of ankles and shortness of breath on least exertion lately. Stated that some years before pulse was very irregular.

Admitted to hospital, April 14, 1923. Slight exophthalmos and lagging of eyelids. Moderate tremor and general nervousness. Uniform enlargement of thyroid gland, with more marked enlargement of isthmus. Heart not found to be enlarged, systolic murmur at apex. Pulse-rate 80, regular. Basal metabolic rate + 5 per cent. For two weeks lost weight and complained of mental unrest and palpitations. May 10, 1923: Partial thyroidectomy. Section showed changes typical of exophthalmic goitre. Immediately after operation found to have auricular fibrillation. Digitalis commenced. May 13: Normal rhythm returned.

Case No. 3. T. R., male, aged 39 years.

History of shell-shock in 1919, and three months later onset of sweating and tremors. In July 1922 swelling in neck noticed, and a month later eyes became prominent. In November 1922 shortness of breath and palpitations commenced, and since then lost weight steadily.

Admitted to hospital, April 24, 1923. Thin, nervous man, sweating profusely, and changing colour easily. Marked exophthalmos and lagging of eyelids. Pronounced tremor of hands, tongue, and face. Thyroid gland showed considerable diffuse enlargement. Heart moderately enlarged, and apex-beat diffuse and forcible. Pulse-rate 100-110, regular. Basal metabolic rate + 61 per cent. May 4, 1923: Partial thyroidectomy, and after operation auricular fibrillation present. May 12, 1923: Normal rhythm returned. May 25, 1923: Basal metabolic rate + 33 per cent. Discharged from hospital, May 28, 1923. Pulse-rate 90-110, regular.

Case No. 4. N. W., female, aged 37 years, married.

History of shortness of breath and palpitations, commencing in August 1921, swelling of ankles in November 1921, and swelling of neck in February 1922.

Admitted to hospital, March 7, 1923. Slight exophthalmos and lagging of eyelids. Somewhat excited, tremors marked. Thyroid gland showed moderate diffuse enlargement. Heart not found to be enlarged. Pulse-rate 90, regular. Basal metabolic rate + 50 per cent. March 9, 1923: Partial thyroidectomy, and after operation auricular fibrillation present. Ventricular rate 130. Commenced digitalis. March 12: Normal rhythm returned.

Case No. 5. J. P., male, aged 50 years.

History of nervousness and loss of weight for one year before admission. Lately, pains in region of heart and muco-purulent sputum.

Admitted to hospital, May 24, 1923. Anxious, slightly staring appearance. No exophthalmos, but lagging of eyelids and weakness on convergence. Thyroid gland moderately and diffusely enlarged. Heart slightly enlarged, apex-beat diffuse and forcible, $3\frac{3}{4}$ in. from mid-line in 5th space. Gingivitis present and several teeth showed apical infection. Basal metabolic rate + 30 per cent. Auricular fibrillation and ventricular extra-systoles present. Ventricular rate 80-100. Discharged from hospital, July 7, 1923.

Case No. 6. K. S., female, aged 47 years, married.

History of tremors and swelling in neck since 1905. Severe tonsillitis 1911. Jaundiced 1914, and operation for gall-stones, but none found. Influenza 1919, and since then palpitations and shortness of breath on exertion. Lately attacks of pain in region of heart and orthopnoea.

Admitted to hospital, June 9, 1923. Thin, and looked tired. Staring appearance, but no exophthalmos nor other eye signs. Tremors of hands and tongue present. Thyroid gland diffusely enlarged. Apex-beat in 4th space, $5\frac{1}{2}$ in. from mid-line. No evidence of valvular disease. Much pyorrhoea and gingivitis and severe apical infection of teeth. Basal metabolic rate + 29 per cent. Auricular fibrillation present. Ventricular rate 110-170. On digitalis, ventricular rate fell to 80 and general condition was much improved.

Case No. 7. A. S., female, aged 45 years, married.

History of swelling in neck and shortness of breath on exertion since August 1919. Tremors and mental distress commenced shortly after. Teeth extracted in November 1919.

Admitted to hospital, March 16, 1920. Very nervous, marked sweating, and changes colour readily. Tremors of hands, tongue, and most of the body. Staring appearance, slight exophthalmos and lagging of eyelids. Thyroid gland greatly enlarged, especially on right side. Heart showed slight enlargement. Pulse-rate 80-90, regular. Slight improvement on general treatment. Discharged from hospital, April 28, 1920.

Readmitted, September 27, 1920. Heart enlarged, apex-beat in 5th space, $4\frac{1}{2}$ in. from mid-line. Auricular fibrillation present. Ventricular rate 100. Digitalis commenced and ventricular rate fell to 80-90. October 14: Partial thyroidectomy. November 2: Further partial thyroidectomy. Discharged from hospital, November 26, 1920. Auricular fibrillation still present. Ventricular rate 70-80. To continue digitalis.

Reported, January 24, 1921. Feeling well and rapidly increasing capacity for exertion. Normal rhythm, rate 50-60.

Case No. 8. S., female, aged 29, single.

History of exophthalmic goitre since 1919, when operation was advised. In 1921 had palpitations on the least exertion and later nervousness and flushings. Swelling in neck then noticed and tremors developed. Pulse-rate 130-140, fell to 80 with general treatment. In February 1922 mother died; condition became much worse and auricular fibrillation reported to be present. Seen by T. P. D., May 10, 1922. Appeared anxious, restless and exhausted. Marked exophthalmos and tremors. Apex-beat well outside nipple-line, and rhythm completely irregular. June 10, 1912: Partial thyroidectomy. August 14, 1922: Further partial thyroidectomy. Auricular fibrillation reported present. October 28, 1922: Increasing capacity for exertion. Walking with comfort. Doctor reported heart always regular.

Case No. 9. R. I., female, aged 48 years, single.

History of six weeks in bed because of condition of heart in 1914. Severe palpitations in 1915. Auricular fibrillation reported to be present in 1916.

Ankles swollen after exercise in 1920, and heart noted to be still irregular. Exophthalmic goitre suggested as cause of heart condition in 1916. Seen by T. P. D., August 7, 1922, when patient had been in bed for eight weeks. Eyes staring, but little exophthalmos. Eyelids drawn up and lagging present. Forehead not wrinkling. No tremors. Thyroid gland enlarged. Marked venous pulse in neck and veins distended. Skin hot and moist. Orthopnoea and oedema of ankles present. Apex-beat just outside nipple-line. Heart's action very rapid and completely irregular. No evidence of valvular disease. August 10, 1922: Partial thyroidectomy. Gland showed changes typical of exophthalmic goitre. August 22, 1922: Heart's action regular. Oedema and dyspnoea much less. May 5, 1923: Doctor reported that patient could walk one or two miles and go upstairs without discomfort, that there was no oedema or dyspnoea, and that the pulse was regular and the rate 72-84.

Case No. 10. H. R., male, aged 40 years.

History. Said to have had exophthalmic goitre for five years and to have had 'myocarditis and irregular heart' for about the same time. In October 1920 a partial thyroidectomy was performed without much improvement. Recently signs of heart failure had been more pronounced, and immediately before admission was under treatment in the National Heart Hospital and the heart failure improved rapidly on rest and digitalis.

Admitted to hospital, October 18, 1922. A thin man, with moderate degree of general nervousness and slight exophthalmos, more marked on left side. No other eye signs, slight tremor. Apex-beat in 5th space, $4\frac{1}{2}$ in. from mid-line. Ventricular rate 80-90, no pulse deficit. Basal metabolic rate + 44 per cent. October 26, 1922: Further partial thyroidectomy. November 15, 1922: Auricular fibrillation still present. Ventricular rate 70. Basal metabolic rate + 4 per cent. Commenced quinidine sulphate v gr. t. i. d., and after four doses sinus rhythm returned. Quinidine continued for further ten days in decreasing doses. July 1923: No return of auricular fibrillation. Increase in efficiency and capacity for exertion had been slow. Could go for walks of 3-4 miles without discomfort, but occasional extra-systoles noted, and on one occasion pulsus alternans as shown by polygraphic tracings (H. J. Starling).

Case No. 11. H. C. W., male, aged 49 years.

History of prominent eyes and palpitations in 1908 following influenza. Said to have had transient attack of auricular fibrillation in 1910. Following an attack of ptomaine poisoning and the death of his father in 1915, became much worse, eyes very prominent, pulse-rate up to 240, and swelling of legs. By 1918 he was much improved and could walk 4-5 miles. In 1922 was in bed for four months following death of son, eyes very prominent, sleeping badly and heart-rate rapid and irregular. Seen by T. P. D. on January 4, 1923. Very nervous and excitable, marked exophthalmos and pronounced tremors. Skin moist. Thyroid gland greatly enlarged and symmetrical. Pulse-rate at radial artery 88, completely irregular and large pulse deficit. Slight oedema of ankles. Lungs clear. Commenced digitalis. January 27, 1923: Partial thyroidectomy. February 10, 1923: Heart still irregular. Further partial thyroidectomy. March 1, 1923: Commenced quinidine sulphate v gr. t. i. d. March 5, 1923: Increased to vijss. gr. t. i. d. March 8, 1923: Increased to x gr. four times a day. March 11, 1923: Heart regular, and quinidine gradually reduced. March 19, 1923: Heart irregular for a day after much worry. March 20, 1923: Out of bed and travelling around London on urgent business. March 31, 1923: Occasional extra-systole. October 20, 1923: Heart quite regular. Efficiency steadily increasing.

Case No. 12. E. G., female, aged 45, single.

History of onset of nervousness, tremor, tachycardia, exophthalmos, and goitre six years before admission. General improvement on various lines of treatment, but lately signs of increasing heart-failure and cardiac irregularity.

Admitted to hospital, July 9, 1922. Slight nervousness, no tremor, marked exophthalmos and lagging of eyelids. Moderate diffuse enlargement of thyroid gland. Apex-beat in 5th space, $4\frac{1}{2}$ in. from mid-line. Auricular fibrillation present. Ventricular rate 120. Orthopnoea, ascites, oedema of legs, back, and bases of lungs. Responded well to rest and digitalis, and was discharged August 8, 1922, greatly improved, but exophthalmos as before.

Readmitted, September 26, 1922, for treatment with quinidine. Ventricular rate 70-90, no pulse deficit. Basal metabolic rate + 26 per cent. October 12, 1922: Commenced quinidine sulphate *vij ss. gr. t. i. d.* Normal rhythm after six doses. November 8, 1922: Quinidine stopped. November 28, 1922: Pulse-rate 70-80. Well, except for severe cough with inflammatory appearances of pharynx and larynx. Exophthalmos as before. Discharged from hospital.

Readmitted, January 29, 1923, because of severe cold. Auricular fibrillation. Ventricular rate 120. Nervousness more pronounced and tremor present. Basal metabolic rate + 44 per cent. February 8, 1923: Ventricular rate 80, as result of rest and digitalis. Commenced quinidine sulphate *v gr. t. i. d.* February 11, 1923: Sinus rhythm, but frequent extra-systoles and faintness. Electrocardiograms showed auricular and ventricular extra-systoles, and variations in auricular complex. February 19, 1923: Auricular fibrillation, though still on quinidine. February 22, 1923: Partial thyroidectomy. March 1, 1923: Auricular fibrillation was still present. Digitalis since February 21. Ventricular rate 80. Digitalis stopped, and commenced quinidine sulphate *v gr. t. i. d.* Stable normal rhythm restored after four doses. March 14, 1923: Basal metabolic rate + 25 per cent.

Discharged from hospital to continue quinidine. July 25, 1923: Sinus rhythm had persisted on decreasing doses of quinidine, except on one occasion when, after severe exertion, auricular fibrillation returned for a few days. An occasional extra-systole noted, but felt better and stronger than for many years.

Case No. 13. E. B., female, aged 60 years, married.

History of weakness since 1919. Told she had exophthalmic goitre in 1921. May 1922, oedema of legs, irregular pulse, and often confined to bed.

Admitted to hospital October 23, 1923. Thin, cheerful woman, liable to periods of depression. Moderate tremor, slight exophthalmos and lagging of eyelids. Moderate enlargement of thyroid gland. Heart not enlarged, auricular fibrillation present, ventricular rate 90-100. No objective signs of heart failure. Basal metabolic rate + 53 per cent. On digitalis, ventricular rate 60-80. November 18, 1922: Partial thyroidectomy. November 29, 1922: Discharged from hospital. Pulse still irregular.

Readmitted February 24, 1923. Slight improvement in general condition. Basal metabolic rate + 47 per cent. Auricular fibrillation, ventricular rate 80-90, on digitalis. March 8, 1923: Further partial thyroidectomy. March 24, 1923: Discharged. Auricular fibrillation, ventricular rate 70-80.

Readmitted June 11, 1923. Had been very weak since discharge. Shortness of breath on exertion and swelling of legs. Auricular fibrillation, ventricular rate 60-70, numerous extra-systoles, sometimes coupling. June 20, 1923: Commenced quinidine sulphate, *ij ss. gr. t. i. d.* June 21, 1923: Increased to *v gr. t. i. d.* June 25, 1923: Normal rhythm. June 28, 1923: Marked sinus arrhythmia and feeling of weakness and faintness. Quinidine stopped. June 30, 1923: Died suddenly.

Case No. 14. L. B., female, aged 46, married.

History of a large goitre as long as she could remember. August 1922: Gradual onset of palpitation and shortness of breath.

Admitted to hospital September 18, 1922. Pale, thin woman, easily disturbed by events in the ward. Skin moist, slight tremor of hands. Orthopnoea, oedema of ankles and bases of lungs. Many carious teeth, and chronic infection

of tonsils. No exophthalmos nor other eye signs. Very large multiple adenomatous goitre on both sides. Apex-beat diffuse in 5th space, $4\frac{1}{2}$ in. from mid-line. Auricular fibrillation, ventricular rate 180. October 8, 1922: Responded well to digitalis. Ventricular rate 84. October 12, 1922: Refused operation. Commenced quinidine sulphate v gr. t. i. d. October 14, 1922: Sinus rhythm, but very irregular, and during next few days auricular extra-systoles, ventricular extra-systoles, varying auricular complexes and auricular flutter noted. October 19, 1922: Quinidine increased to vij ss. gr. t. i. d. October 23, 1922: Dizziness and faintness: quinidine reduced to v gr. t. i. d. October 28, 1922: Basal metabolic rate + 50 per cent. November 6, 1922: Basal metabolic rate + 35 per cent. Rhythm still disturbed by numerous extra-systoles. November 27, 1922: Severe tonsillar abscess, diffuse purpuric eruption, return of auricular fibrillation, quinidine stopped. November 29, 1922: Digitalis commenced. Purpura subsiding. Quinsy incised. November 30, 1922: Aphasia and incomplete right-sided hemiplegia. December 5, 1922: Aphasia and hemiplegia passing off. December 21, 1922: Auricular fibrillation still present, ventricular rate 70-80. Quinidine sulphate v gr. t. i. d. December 28, 1922: Sinus rhythm, occasional extra-systole. January 9, 1923: Teeth extracted. Rhythm not disturbed. January 28, 1923: Tonsillectomy. Rhythm not disturbed. June, 1923: Sinus rhythm had persisted. Had continued on quinidine v gr. t. i. d. Pulse-rate 80-90. Working as a cook.

Case No. 15. A. O., female, aged 49 years, married.

History of weakness, tremors, loss of weight, and goitre when 33 years old. Under treatment off and on since, worse lately.

Admitted to hospital November 21, 1922. Nervous, moderate tremor, pronounced flushing. Eyes glistening, no exophthalmos nor other eye signs. Thyroid gland moderately enlarged. Tonsils enlarged and ragged. Auricular fibrillation, ventricular rate 190. Sinus rhythm returned after 24 hours, pulse-rate 110-120. Basal metabolic rate + 41 per cent. January 8, 1923: Basal metabolic rate + 10 per cent. January 20, 1923: Pulse-rate 80-90. Marked general improvement. Discharged.

Reported April 26, 1923. Condition as on admission in November 1922. Auricular fibrillation, ventricular rate 170. Commenced digitalis as out-patient. May 3, 1923: Auricular fibrillation still present. Ventricular rate 144. Commenced quinidine sulphate v gr. t. i. d. May 10, 1923: Sinus rhythm, and this had persisted on each occasion since, when patient had reported. Extra-systoles noted at times, and patient stated that she had had return of auricular fibrillation for a few hours on several occasions. Quinidine had been continued. When sinus rhythm was present, heart-rate had varied from 104 to 130. No decided improvement noted, except that patient stated she was less comfortable when auricular fibrillation was present.

DESCRIPTION OF PLATE.

PLATE 20, FIG. 1. Case No. 3. Partial thyroidectomy. 4.5.23.

- (a) Lead II. 7.5.23. Auricular fibrillation.
- (b) Lead II. 18.5.23. Sinus rhythm returned spontaneously.

FIG. 2. Case No. 14.

- (a) Lead II. 20.10.22. Auricular fibrillation.
- (b) Leads I, II, III. 26.10.22. Unstable sinus rhythm resulting from quinidine: numerous ventricular extra-systoles, and probable auricular flutter in Leads II and III.
- (c) Chest Lead. 6.11.22. Same as in (b). Succession of ventricular extra-systoles.
- (d) Lead II. 18.1.23. Stable sinus rhythm resulting from quinidine after recovery from acute infection and improvement in thyro-toxic condition.

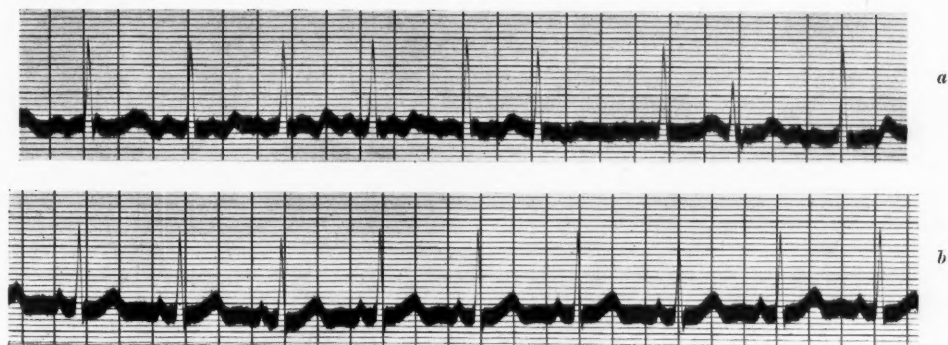


FIG. 1

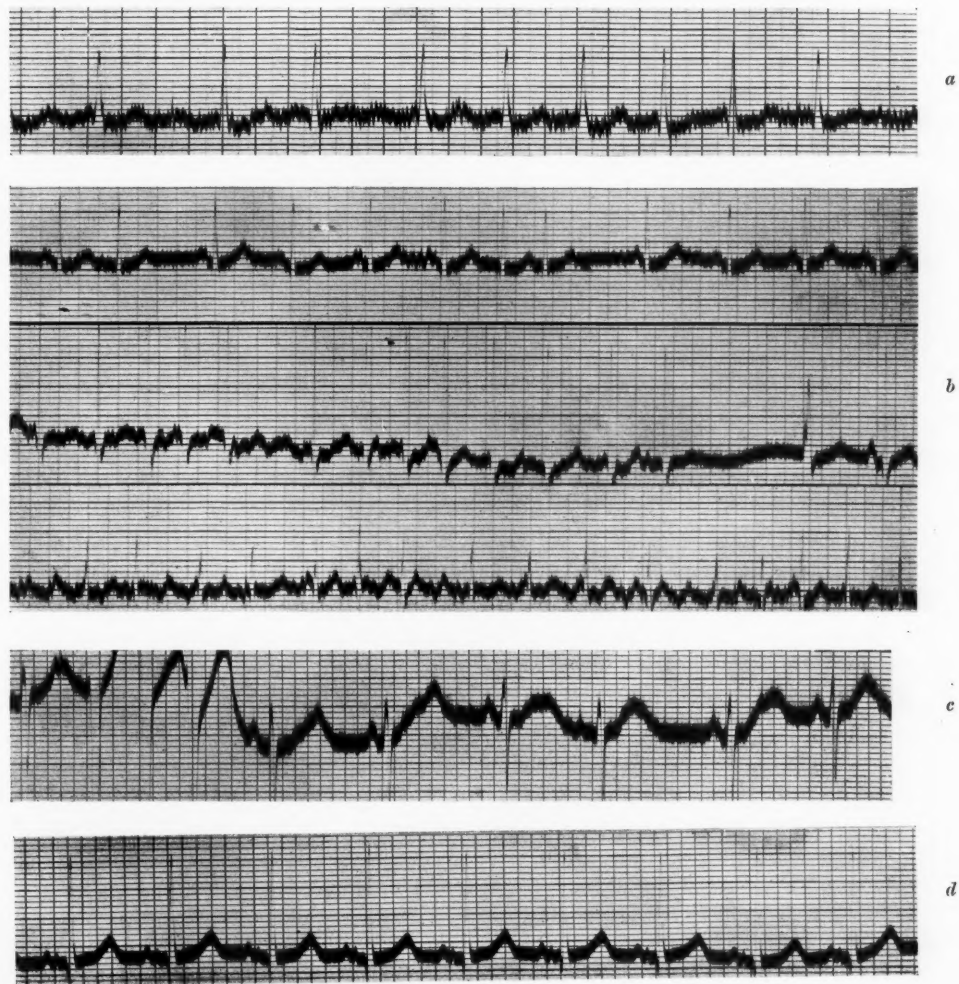


FIG. 2



A STUDY OF THE METABOLISM IN THE UNDER-NOURISHED INFANT

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Introduction.

THE infants examined in this study were admitted to hospital in various degrees of malnutrition. In each case, specific morbid conditions, such as tuberculosis, congenital syphilis, or chronic inflammatory mischief, were excluded as far as possible, so that the condition appeared to be due to nutritional causes only. Further, only those cases were investigated in which no gastro-intestinal disturbances were present, so that they resembled those usually designated as marasmus, infantile atrophy, athrepsia, dystrophy, or decomposition.

Most of the modern writers on the subject freely admit that gastro-intestinal disturbance plays a prominent part in the causation of infantile atrophy, but there are some who regard the condition as being due to defective tissue metabolism or some functional defect. Thus Marfan (13) assumes that in the infant the intestinal and tissue enzymes (trophozymases) are less abundant and less active than in the adult, and that this deficiency is corrected by certain specific enzymes in human milk. In infants deprived of the breast, these trophozymases may not be able to bring about correct anabolic and katabolic processes. Uthelm (19) believes that the diminished flow of blood in atrophic infants lowers the metabolism, and that this leads to deficient utilization of food, especially of protein and salts, and to the excretion of their unmetabolized constituents in the urine. Such ideas cannot, in the present state of our knowledge, be definitely formulated so far as the abnormal chemical processes are concerned, but it may be presumed that in such circumstances the defective utilization of food in the tissues, the lowered metabolism, and the defective ferment action would manifest themselves in disturbances in the metabolic rate or in the presence of abnormal substances in the excretions.

Czerny (15) postulates a defective absorption of fat with a consequent excess of fatty acids in the gut. He thinks that these acids are neutralized by calcium to form calcium soaps, and, in severe cases, that there may even be an abstraction from the tissues of sodium and potassium, which are excreted

into the gut. In his opinion, this demineralization of the body leads to a lowering of available fixed alkalies in the tissues, and hence to an acidosis or alkalipenia, the acidosis showing itself by an increased ammonia output in the urine. In connexion with this theory, an excessive fat content in the faeces has not been demonstrated, while the ammonia output in the urine is but slightly increased. Finally, the first sequel of diminished fat absorption, viz. increased faeces bulk, is not found.

Finkelstein (4) is of opinion that infantile atrophy may be brought about in several ways, and arranges his classification accordingly. The stage of dystrophy he attributes to functional inability of the intestinal epithelium to absorb fat, and the same objections may be made to this suggestion as have been raised against the hypothesis of Czerny. In the stage of dyspepsia he considers there is a lowered tolerance to carbohydrate, which undergoes abnormal fermentation with increased rapidity in the passage of the contents through the gut. It is at this stage that Finkelstein first admits gastro-intestinal disturbance, but, as mentioned above, we do not propose to deal with such cases, for in them the error lies in the digestion of food, which is not suitably prepared for absorption and consequently never reaches the tissues.

Marriott (14) bases his views on the assumption that some children when on a diet of cow's milk are unable to secrete the amount of HCl necessary to bring the gastric contents to the optimum H-ion concentration. This leads to diminished secretin formation and diminished secretion of pancreatic juice. Hence, there is a delay in the passage of stomach and upper intestinal contents, and this provides suitable conditions for the invasion of *B. coli* into the upper intestinal tract. This view, then, attributes atrophy to gastro-intestinal disturbance. It assumes a constitutional factor which cannot be proved and a diminished pH of the gastric contents which has not as yet been demonstrated. He believes, however, that the ultimate cause of the condition is an excess of caloric output over intake, acting over a prolonged period.

All these views assume a constitutional factor, such as a deficiency in tissue enzymes, inability to retain water, defective power of fat absorption, or inability to secrete sufficient gastric juice; or they assume a gastro-intestinal disturbance with sequelae such as loss of food, salts, and water, sequelae which would obviously prejudice nutrition without having recourse to a further cause. No attempt is made in this study to explain the causes of gastro-intestinal disturbance, but data are put forward from which the value of certain of the above hypotheses may be estimated.

There are three, and only three, factors which may cause failure to thrive. These are:

1. Defective absorption of food.
2. Defective utilization in the tissues of absorbed food.
3. Excessive combustion of absorbed food.

We have endeavoured to test the first factor by studying the retention of the proximate principles of the food by balance experiments. By respiratory

exchange experiments and examination of the urinary constituents we have tested the second possibility; and by examination of the basal metabolism we have endeavoured to investigate the last.

Notes of the various methods employed in this investigation are given in an appendix.

Absorption of Food.

It is absolutely necessary at the outset to differentiate between a true defective absorption, due to a loss of the inherent power of the bowel-wall to absorb food material, and a defective absorption caused by increased fermentation and increased peristalsis of the gut whereby the bowel-wall does not get the opportunity of absorbing the food-stuffs. In the latter case, the cause of the wasting is not to be found in a defective power of absorption, but in abnormal chemical processes in the bowel contents; and it becomes necessary to explain these abnormal processes in order to arrive at the pathogenesis of the condition. Hence, in studying the ability of the gut to absorb we have only utilized cases in which there was no gastro-intestinal disturbance. In the second place, it is most important to decide how best to gauge normal absorption. Until the present it has been customary to judge the normality or otherwise of absorption from the percentage of intake absorbed. We are of opinion that such a method may give an entirely wrong impression.

TABLE I.

Intake of Fat. Grm.	Output of Fat. Grm.	Retained. Grm.	% Absorption.
5	3.5	1.5	30.0
10	3.5	6.5	65.0
15	3.5	11.5	76.6
20	3.5	16.5	82.5
25	3.5	21.5	86.0
30	3.5	26.5	88.3

The absorption of fat illustrates this point. The percentage absorption of fat must depend on the fat intake and on the fat output. A certain amount of fat is always present in the faeces. The fact that it forms fairly constantly about 33 per cent. of the dried faecal weight shows that the fat output must depend on the faeces weight. The greater the faeces weight, the greater the output of fat, and vice versa: hence the percentage of intake absorbed will vary inversely as the faeces weight. The daily variation in faeces weight, and consequently in fat output, may be lessened by making the period of observation sufficiently long or by taking the mean of a large number of observations. It is only when the faeces weight is rendered more constant in this way that the percentage absorption will tend to become at all a reliable index of absorption. But the influence of the intake must also be considered. It will be seen from Table I that with a constant fat output and a varying fat intake the actual amount of fat absorbed bears no relation to the percentage absorption. This is important because one frequently finds the atrophic child fed on much smaller

quantities of fat than the healthy child. Hence, if one is to compare the percentage absorption in health and marasmus the intake and faecal weight must be the same in both.

These points will be referred to below in considering the results in detail. They have been argued in connexion with fat for the sake of convenience, but they are equally applicable to the other food-stuffs.

Fat Absorption.

Observations were made on four healthy and eight marasmic children, each experiment lasting for a period of at least 3 days. (In the healthy children the fat intake was varied intentionally in order to determine the influence of fat and calcium on faecal weight (Telfer (18)). The results are shown in Table II, where it will be seen that there are considerable variations in the fat output and faeces weight, but that these vary in direct proportion. It may be presumed that the absorption of fat in healthy cases was normal. The faecal weight averaged the same in both and the average fat output was the same in both, but the atrophic subjects retained a mean of 16.8 grm. against a mean of 10.32 grm. for the healthy. This, of course, is due to the fact that the fat intake in the atrophics was greater than in the healthy, for had the healthy subjects received the same amount of fat as the atrophic they would have absorbed a mean of 15.03 grm., supposing that their absorption rate remained constant with the larger intake. This shows that in the atrophic cases there was no defect in the power of absorbing fat.

In Table III are noted the mean results of series of cases examined by Holt (7), Uthaim (19), and one of us (9). Those of Holt were calculated from a certain number of his cases where the faecal weight (which was not shown) could be estimated. Uthaim's data were not sufficient for this to be done, but the intake and output are shown. It is unfortunate that she has not noted the faeces weights. She states that 'the weight of the stools has not been determined', and it would be interesting, in view of this, to know how the total output was arrived at.

By taking the means of these series of cases, the daily faeces weight has been reduced to approximately the same level in all, and the percentage absorption is then seen to vary directly with the fat intake; and further, if we omit one case in Uthaim's series, which gave an obviously pathological result with an excretion of 11.2 grm. of fat, her mean daily output falls to 4.21 grm., which is practically the same as in the other series.

These facts receive additional support from Cases 5 and 9, Table II, where fat in increasing quantities was supplied to two under-nourished infants on the supposition that, if absorption were defective, any increased intake would lead to an increased loss. In Case 9 the fat intake was raised from 17.7 grm. (period 1) to 35.5 grm. (period 3) and the retention rose from 15.7 grm. to 33 grm.: thus by doubling the intake the retention was doubled. In Case 5

TABLE II.

Fat Balance in Healthy and Marasmic Children.

Case.	Period.	Mean Faeces Weight. Grm. per day.	Fat Intake. Grm. per day.	Fat Output. Grm. per day.	Fat retained. Grm. per day.	Percentage Absorption.
<i>Healthy.</i>						
1	1	18.5	20.7	7.43	13.27	64.1
	2	3.7	1.3	1.13	0.17	13.0
	3	4.9	1.3	0.51	0.79	60.7
	4	10.0	15.5	3.57	11.93	76.9
	5	10.2	15.5	4.4	11.10	71.6
2	1	10.2	17.4	3.71	13.69	78.6
	2	6.1	8.7	2.53	6.17	70.9
	3	2.0	1.7	0.5	1.2	70.5
3	1	10.5	18.2	4.35	13.85	76.1
	2	16.3	18.7	6.68	12.02	64.2
	3	21.5	10.0	9.67	0.33	3.3
	4	8.5	25.0	2.78	22.22	88.8
	5	11.5	21.0	2.85	18.15	86.4
4	1	7.2	19.9	1.87	18.03	90.6
	2	9.8	15.2	3.31	11.89	78.2
Mean		10.0	14.0	3.68	10.32	73.7
<i>Marasmic.</i>						
5	1	8.4	16.7	3.47	13.23	79.2
	2	7.9	27.0	3.75	23.25	86.1
	3	14.8	37.2	8.9	28.30	76.0
6	1	10.0	6.3	2.05	4.25	67.4
	2	6.9	8.0	1.43	6.57	82.1
	3	17.3	20.8	6.02	14.78	71.0
	4	12.3	21.3	4.9	16.40	76.9
7	1	10.0	19.8	2.65	17.15	86.6
	2	8.5	19.8	3.57	16.23	81.9
8	1	12.7	20.5	4.52	15.98	77.4
9	1	9.9	17.7	1.97	15.73	88.8
	2	11.0	28.5	3.93	24.57	86.2
	3	9.1	35.5	2.46	33.04	93.0
10	1	9.4	20.9	3.49	17.41	82.8
	2	6.6	25.7	2.25	23.45	91.2
	3	7.7	6.1	1.74	4.36	71.8
11	1	14.8	21.2	5.8	15.40	72.6
	2	11.3	13.3	4.11	9.19	69.1
12	1	6.8	23.4	2.14	21.26	90.8
Mean		10.2	20.4	3.6	16.8	84.3

TABLE III.

Author.	Case.	Faeces Weight. Grm. per day.	% Fat in Dried Faeces.	Intake of Fat. Grm. per day.	Output of Fat. Grm. per day.	Retention. Grm. per day.	Percentage Absorption.
Hutchison	Healthy	10.0	36.8	14.0	3.68	10.32	73.7
Hutchison	Marasmus	11.9	35.1	17.8	4.18	13.62	76.1
Utheim	Marasmus	—	—	19.5	4.6	14.9	77.0
Hutchison	Marasmus	10.2	35.2	20.4	3.6	16.8	84.3
Holt	Healthy	7.3	34.2	23.7	2.5	21.2	89.4
Hutchison	Healthy	9.9	33.3	35.2	3.3	31.9	90.6

evidence of defective absorption appeared in the third period, but even here an increase of 20.5 gm. in fat intake over the normal for age led to an increased retention of 15 gm.

By using figures showing the total fat intake, loss, and retention, rather than relying on percentage figures, it seems clear that there is no defect in the power of atrophic infants to absorb fat.

Nitrogen Assimilation.

A. *Nitrogen absorption.* The absorption of nitrogen in healthy children is very good, and varies from 80 to 95 per cent. of the intake. Disturbances of nutrition appear to affect but little the absorption of this element. In marasmic infants it has repeatedly been shown that the absorption of nitrogen is not disturbed. Much of the work on this subject is well reviewed by Von Noorden (16), and he shows that the percentage of nitrogen in the faeces is fairly constantly between 5 and 6 per cent. of the dried faecal weight. The mean faeces weight in the series of cases examined by us was 10.9 gm., hence one would expect the mean nitrogen output to lie between 0.54 and 0.64 gm. per day. In the ten cases of this series the mean was 0.57 gm. Table IV shows the output of nitrogen and also the percentage absorptions. Here again it will be noticed that the faecal output of nitrogen varies directly with the faeces weight, and that the percentage of nitrogen in the dried faeces is remarkably constant.

TABLE IV.

The Output of Nitrogen per 24 Hours and Percentage Absorption of Nitrogen in Marasmus.

Intake. Grm. per 24 hours.	Nitrogen retained. Grm.	Faeces Weight. Grm.	Output of Nitrogen. Grm.	% of Nitro- gen in Dried Faeces.	% Absorption.
2.39	1.77	11.3	0.62	5.4	74.0
3.47	2.77	14.8	0.70	4.7	79.8
3.61	3.14	9.8	0.47	4.8	86.9
3.79	3.38	6.8	0.41	6.0	89.1
4.00	3.48	9.1	0.52	5.7	87.0
4.14	3.28	15.25	0.86	5.6	79.2
4.27	3.81	9.9	0.46	4.6	89.2
4.32	3.75	11.0	0.57	5.1	86.8
4.79	4.31	9.45	0.48	5.0	89.9
4.83	4.17	11.7	0.66	5.6	86.3
3.96	3.38	10.9	0.57	5.2	85.0 Mean

This table shows the fallacy of regarding percentage absorption as an index of absorption. In Uthelm's cases, though less nitrogen was lost than in ours, the percentage absorption was less, and this is clearly dependent on the smaller intake, which was 1.96 gm. as compared with 3.96 gm. Healthy controls were not included in our series, but the absorption of nitrogen in marasmus may be regarded as normal, since the percentage of nitrogen in the dried faeces corresponds closely to the figures given by Tschernoff (16) and the mean faeces weight is the

same as in the healthy child. If one takes the percentage figures, the present result of 85 per cent. falls within the normal limits quoted above. Our results therefore appear to confirm the previous work on the subject, that the absorption of nitrogen in marasmus is in no way impaired.

B. *Nitrogen balance.* In order to examine the assimilation of protein, ten balance experiments, each lasting from two to six days, were carried out on six marasmic infants. During five of these experiments the subjects gained weight and in three they lost weight, while in two the weight was stationary. The degree of marasmus varied, but in all the weight was considerably below normal. The nitrogen determinations were made on the wet faeces in order to obviate the possibility that nitrogen might be lost during the process of drying. Daily estimations were made in each case, but the means only of each period are shown. The results are shown in Table V :

TABLE V.
The Nitrogen Retention in Marasmus.

Case.	Period.	Duration of Experiment. Days.	Gain or Loss in Weight. Grm.	Urine Output. c.c. per day.	Mean N. Intake. Grm. per day.	Mean N. in Urine. Grm. per day.	Mean N. in Faeces. Grm. per day.	Total N. Output. Grm. per day.	N. retained. Grm. per day.
9	1	6	+290	429	4.27	3.06	0.46	3.52	+0.75
	2	2	+110	547	4.32	3.56	0.57	4.14	+0.18
	3	3	+60	499	4.00	3.24	0.52	3.76	+0.24
13	1	4	± 0	347	4.79	2.69	0.48	3.17	+1.62
14	1	5	-40	134	3.47	1.10	0.70	1.80	+1.67
	2	3	+30	173	2.39	0.38	0.62	1.00	+1.39
16	1	4	+100	359	3.79	1.63	0.41	2.04	+1.75
15	1	2	± 0	230	4.83	1.25	0.66	1.91	+2.92
	2	4	-60	274	3.61	1.72	0.47	2.19	+1.42
17	1	4	-50	810	4.14	2.68	0.86	3.54	+0.60
Mean				380	3.96	2.13	0.57	2.71	+1.25

From this table it will be seen that, in all cases, irrespective of whether the weight was rising, stationary, or falling, the nitrogen balance was positive. This is probably due to the large intake of nitrogen in nearly all the cases.

The nitrogen output on a constant nitrogen intake was determined in seven subjects (Table VI). Case 15 of Table V is included in this series. The important fact shown in these results is that there was an increase in the urinary nitrogen with improvement in the nutritional state.

Previous work on nitrogen metabolism has established that after prolonged malnutrition the loss of body protein sinks to a minimum, because the body tends to economize its protein as far as possible (Lusk, 10). If the body does not receive enough nitrogen it no longer remains in nitrogenous equilibrium, and a negative balance of nitrogen appears until such time as the lessened nitrogen and caloric intake is sufficient to equalize the output. It has been specially stated 'lessened nitrogen and caloric intake', because a diet containing an adequate amount of protein (such as a milk and water mixture) may still be of insufficient caloric

value, and though a diet of this kind can diminish, or even for a time postpone, the loss of nitrogen, the result in the long run will be the same as if all the components of the diet were diminished. When, owing to wasting, the nitrogen requirements are reduced so that they are supplied by the nitrogen intake, small though it is, then nitrogenous equilibrium is established at a lower level. If, now, an increased amount of food be given so that the deficiency of caloric intake is reduced, the body at once retains what nitrogen it can in order to replace the loss of cellular material, and this goes on until the body has readjusted itself to the new conditions of nutrition, and nitrogenous equilibrium has been established. This is well shown by Benedict (1) in a subject recuperating after complete starvation. It is clear, then, that during recuperation there will be a gradually decreasing nitrogen retention and increasing nitrogen excretion.

TABLE VI.

To show the Increased Nitrogen Output in Marasmus with an Improvement in the Nutritional State. N. Intake constant.

Case.	Period.	Weight. Gm.	c.c. Urine per 24 hours.	Total Urinary N. per 24 hours.
15	1	3630	230	1.25
	2	3860	274	1.72
18	1	3593	500	2.12
	2	3810	373	2.18
19	1	4030	405	2.16
	2	4042	289	2.20
	3	4312	438	2.44
20	1	3880	204	2.00
	2	4257	250	2.29
	3	4340	286	2.46
9	1	3811	429	3.06
	2	4256	518	3.39
22	1	5066	325	3.23
	2	5160	289	3.44
	3	5280	237	3.61
21	1	3670	282	1.92
	2	3690	316	1.96
	3	4242	563	3.84
	4	4600	576	3.24

In the experiments shown in Table VI the nitrogen intake during the different periods was kept constant in each subject. The increasing output of nitrogen on this constant intake is well seen, and this, on the grounds mentioned above, would strongly suggest a previous state of relative starvation. Case 21 is particularly instructive, though it does not come within our category of atrophy, as there was a definite cause for the wasting. It was a case of rumination, and this had led to most severe malnutrition. During the four periods, the nitrogen intake was constant, and the marked rise of nitrogen excretion is very striking. This, of course, was an extreme case, but it serves to explain the others.

The conclusions to be drawn from these experiments are:

1. That in atrophy there is no defect in ability to absorb protein.
2. That in atrophy nitrogen can be satisfactorily retained in the body.
3. The gradual approximation to a condition of nitrogenous equilibrium as recuperation proceeds suggests a previous condition of relative starvation.

The Absorption of Carbohydrate.

Unfortunately, up to the present, it has been found impossible to gauge the absorption of carbohydrate. If carbohydrate remains in the bowel unabsorbed for any length of time, it undergoes fermentation into lactic acid and other substances, and is certainly not excreted in the faeces in the form of carbohydrate. Consequently it is impossible to determine how much of the intake is absorbed. The work of Guy (6) has shown that there is a slightly diminished percentage of sugar in the blood in marasmus, and subsequent work in this department (as yet unpublished) confirms this view. Unfortunately we cannot find any observations on the blood-sugar in starvation, but the general statement is that it falls very slowly and not to any great extent. The organism is very intolerant to a gross diminution in the blood-sugar. We see this with insulin, and no doubt it will use every means possible to regulate this, even to the extent of utilizing protein to provide the necessary carbohydrate. It does not seem strange, therefore, that there should only be a moderate degree of hypoglycaemia in marasmus, for, although carbohydrate may not be well absorbed from the gut, there are considerable amounts of protein being absorbed and the subject is not in a state of complete starvation. We have already shown that in the absence of gastro-intestinal disturbance there is no defect in the power of absorption of protein and fat in atrophy. Probably the same applies to carbohydrate. But of all foods carbohydrate is the one most liable to cause gastro-intestinal disturbance, and it seems likely that in this way it may be at fault.

Caloric Intake and Output.

In order to confirm the above results still further, and to determine whether there is an undue loss of food-stuff by the bowel in atrophy, estimations of the caloric values of the food and faeces were made.

A caloric balance was carried out in each of the cases detailed in Table I, and the results are shown in Table VII. It will again be noted that here, as in the case of fat, the caloric output varied directly with the faecal output, and therefore the same objections to percentage absorptions must be raised in judging of the normality of caloric absorption. It is accordingly proposed to take the actual daily caloric output as the index of normal or abnormal absorption.

Utheim (19) considers that in atrophy there is a relatively large caloric loss in the stools. But, unfortunately, she only deals with the percentage loss. If

absolute quantities be calculated for her cases, there is seen to be less actual loss in her atrophic infants than in her healthy ones.

TABLE VII.

Showing Caloric Balance in Health and Marasmus.

Case.	Period.	Mean Faeces Weight. Grm. per 24 hours.	Intake. Cals. per day.	Output. Cals. per day.	Percentage Absorption.	Total Absorption. Cals. per day.
<i>Healthy.</i>						
1	1	18.5	597	92.1	84.5	504.9
	2	3.7	421	13.6	96.7	407.4
	3	4.9	421	12.6	97.0	408.4
	4	10.0	553	48.1	91.3	504.9
	5	10.2	553	51.9	90.6	501.1
2	1	10.2	605	42.4	92.9	562.6
	2	6.1	538	27.6	94.8	510.4
	3	2.0	348	7.4	97.8	340.6
3	1	10.5	486	57.7	88.1	428.3
	2	16.3	502	81.8	83.7	420.2
	3	21.5	410	110.0	73.1	300.0
	4	8.5	597	41.4	93.0	555.6
	5	11.5	500	51.5	89.7	448.5
4	1	7.2	407	27.4	93.2	379.6
	2	9.8	440	47.0	89.3	393.0
Mean		10.0	491	47.5	90.3	444.0
<i>Atrophy.</i>						
5	1	8.4	326	54.5	83.2	271.5
	2	7.9	477	50.4	89.4	426.6
	3	14.8	549	92.9	83.0	446.1
6	1	10.0	498	41.7	91.6	456.3
	2	6.9	351	25.5	92.7	325.5
	3	17.3	581	90.8	84.3	490.2
	4	12.3	592	61.9	89.3	530.1
7	1	10.0	387	46.1	88.0	340.9
	2	8.5	387	48.3	91.5	338.7
8	1	12.7	515	80.8	84.3	434.2
9	1	9.9	468	37.8	91.9	420.2
	2	11.0	549	58.6	89.4	490.4
	3	9.1	624	42.2	93.3	581.8
10	1	9.4	498	44.2	91.1	453.8
	2	6.6	619	27.3	95.5	591.7
	3	7.7	389	28.6	92.6	360.4
11	1	14.8	517	73.5	85.6	443.5
	2	11.3	530	62.5	88.2	467.5
12	1	6.8	467	43.2	90.7	423.8
Mean		10.2	490	53.2	89.1	436.0

Our results show (Table VII) first of all that, as in the case of fat and nitrogen, the caloric value of the faeces varies directly with the faeces weight, and that the average faeces weight in atrophy is practically the same as in health.

TABLE VIII.

	Mean Cal. Intake per day.	Mean Cal. Output per day.	Calories retained per day.	Percentage of Intake lost.
Utheim.				
Healthy children	791	57.5	734	7.2
Atrophics	443	53.9	390	12.1
Authors.				
Healthy children	491	47.5	444	9.7
Atrophics	490	53.2	436	10.9

In Table VIII is shown the mean caloric intake, output, and absorption in the healthy and atrophic subjects observed by Utheim and ourselves. It will be seen that the caloric loss is approximately the same in all, and that the amount is dependent on the intake. In our series, where the intake by the atrophics was the same as by the healthy, the absorption was almost the same, while in Utheim's series, where the healthy had a far greater intake than the atrophic, the absorption was proportionately greater.

It may therefore be concluded from these results that:

1. The daily caloric loss in the faeces is directly proportional to the faeces weight.
2. The loss of Calories on the average is practically the same in atrophy as in health.
3. An increase in caloric intake leads to a corresponding increase in retention.

The Utilization of Food.

It has been shown in the foregoing sections of this paper that in the absence of gastro-intestinal disturbance there is in marasmus no apparent defect in the absorption of ingested food. We must now consider whether there is any abnormality in the combustion of the food once it has been absorbed. There are two possibilities: either there may be defective oxidation of the food or some part of it, or there may be increased oxidation. In the first case there would be a condition similar to diabetes mellitus, where there is defective oxidation of carbohydrate and fat, while in the second case there would be a condition like that occurring in Graves's disease or in fever, where oxidation is going on too rapidly.

1. *Defective oxidation of food.* If the food is absorbed from the gut but not utilized it must either remain in the body or be excreted. If it remained in the body, the weight would increase, while if it were excreted unoxidized we should be able to detect it in some of the excretions. As the essence of marasmus is that the weight does not increase, it is clear that the food cannot remain in the body. It is possible that small amounts of partially oxidized products of protein metabolism, such as oxypyruvic and other organic acids, may be excreted in the urine in marasmus. Utheim (19) has detected such substances, but from our investigations on the nitrogen metabolism it is clear that there is no gross loss in this way, and, moreover, the caloric value of the urine in Utheim's cases of marasmus was considerably lower than in his well-nourished cases. As regards carbohydrate, we very rarely find sugar in the urine, and that only in very small

amounts. Unaltered fat is never found, and the intermediate products of fat metabolism, such as β -oxybutyric acid, acetone, and diacetic acid, are only present in appreciable amounts when there is almost complete starvation or fever.

As regards the excretion from the lungs, the respiratory quotients that we have observed (5), and those recorded by others (3), do not indicate that there is any failure of oxidation, for if there were any gross defect in oxidation, respiratory quotients widely outside the normal range would inevitably appear.

These results afford strong evidence that failure to oxidize absorbed food does not play a part in the causation of marasmus.

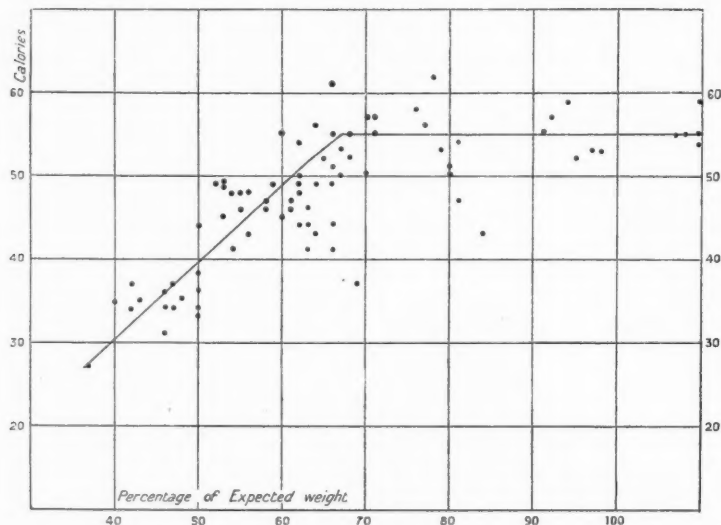


CHART 1. The heat output per kilo of expected weight and the percentage the subjects were above or below expected weight.

2. *Excessive combustion of absorbed food.* It has been shown that undernourished infants, after they become about 35 per cent. below the expected weight¹ for their age, have a basal metabolism² below normal for their age, and that the greater the degree of emaciation the lower the basal metabolism. Series of cases have been published by one of us (5) and by Talbot (17) showing this. In Chart 1 all these observations have been placed together so as to show the degree of emaciation, expressed as percentage of expected weight, and the heat output per kilo of expected weight. By this means we can see the gradual fall in the basal metabolism as emaciation proceeds. It is interesting to compare these with the results found under experimental conditions in man and lower animals. The most extensive piece of work on this subject has been done by Benedict and his

¹ Holt's (8) weight tables have been used to calculate this.

² The so-called basal metabolism in infants is never a true basal metabolism, as, in order to keep them quiet, food has to be given shortly before the commencement of an experiment. Consequently the basal metabolism of infants is almost always the true basal metabolism plus the amount to be added for the specific dynamic action of the food.

co-workers (2). In these experiments two squads of students were subjected to under-nutrition for considerable periods, and during this time their metabolism was examined. The changes in the metabolism during recovery from under-nutrition have been well shown by Magnus-Levy (12) in a youth who had subjected himself to semi-starvation for a prolonged period. Lusk (11) reviews all the work, and shows that with a very small reduction in body-weight, in some cases as little as 6 per cent., there may be a reduction of 32 per cent. in the basal metabolism. These results do not seem to conform to the findings in infants, but a possible explanation of this may be found in the fact that in the cases quoted by Lusk there was an insufficient protein intake, so that there was not nitrogenous equilibrium, and consequently active metabolic tissue was being lost from the start. Moreover, in infants there are relatively much larger reserves of fat than in normal adults. As it seems to be the case that only when the body protein is being drawn upon to supply the vital needs there is a diminution in the basal metabolism, then in infants with relatively large stores of fat the point in the course of emaciation at which the body protein is encroached upon will be lower than in adults. An infant only 20 per cent. below the normal weight for its age is not markedly emaciated, and even when 50 per cent. below weight it is not in the serious predicament that an adult would be in like case. This seems to afford some explanation of the difference found in the adult and in the infants studied by Talbot and one of us.

Recently we have had occasion to examine thirteen other cases, all of which fall into line with those previously published. Three of these, however, were suffering from congenital obliteration of the bile-ducts, one was a case of pyloric stenosis, one was a case of rumination, three were premature, and the remaining five were 'marasmic'. In spite of these various pathological conditions, the rate of the basal metabolism in all corresponded closely with the rate found in uncomplicated marasmus. If marasmus is dependent on a disturbance of metabolism, it is surprising to find patients suffering from other well-defined diseases showing the same disturbance. Certain diseases—diabetes, thyroid disease, and fevers—show well-defined and characteristic disturbances of the basal metabolism, while in marasmus we find a basal metabolism corresponding to that found in many other conditions attended by malnutrition, whether it be brought about experimentally in the laboratory or accidentally by war, famine, or disease. Thus it seems likely that marasmus is not caused by metabolic disturbance, but that the alteration in the basal metabolism is due to the emaciation accompanying marasmus. It seems, therefore, that we must look elsewhere than to disturbance in metabolism for the cause of marasmus.

Table IX and Chart 2 give the results in the thirteen cases mentioned. The same method as that used in Chart 1 has been employed in the construction of this chart. It will be seen that the greater the degree of emaciation the lower is the basal metabolism compared to the normal for the same age (or expected weight). In this chart the various diseases studied are indicated by different signs, and, no matter what the disease, they all show a basal metabolism which

might have been closely predicted from the figures previously published for marasmic infants. In most of the subjects several observations were made, but the mean of the truly basal periods only is shown in Chart 2. Observations in the case of rumination (By.), however, were made in November, February, and April, and each of these is recorded in the chart, for in this case considerable intervals of time elapsed between the observations, and it is of importance to show how the metabolic rate approached normal with the improvement in nutrition.

TABLE IX.

Case.	Age.	Litre CO ₂ per hour.	Litre O ₂ per hour.	Total Cals. per 24 hours.	Cals. per kilo.	Cals. per kilo ex- pected Weight.	Weight. Kilos.	Length. Cm.	Per cent. of ex- pected Weight.	
Ce.	5/52	1.12	1.41	165	63	33	2.6	—	52	Premature
		1.2	1.44	169	63	33	2.65	—	—	
An.	11/52	2.02	1.88	228	85	41	2.68	45	49	Premature
Sl.	2/52	1.23	1.51	177	87	51	2.03	44	60	Premature
	3/52	1.17	1.35	160	77	47	2.07	—	60	
Hl.	26/52	3.13	3.58	424	74	56	5.7	—	76	Pyloric stenosis
	27/52	3.1	3.19	384	68	51	5.65	—	—	
Bn.	12/52	2.29	2.86	330	86	58	3.8	56.5	68	Biliary atresia
	13/52	2.16	2.70	311	83	54	3.72	—	65	
Se.	8/52	2.25	2.76	319	80	50	3.96	55	62	"
Ste.	16/52	1.92	2.61	295	72	47	4.05	57.5	64	"
	16/52	1.71	2.05	238	61	38	3.88	—	63	
By.	56/52	2.57	2.69	324	88	33	3.68	—	38	Rumination
	66/52	3.52	4.09	484	75	48	6.45	—	64	
	73/52	4.17	4.35	523	71	47	7.3	—	66	
Cn.	39/52	3.19	3.43	411	77	51	5.30	60	66	
	40/52	2.97	3.37	400	74	49	5.4	—	66	
De.	20/52	3.12	3.10	376	76	55	4.93	—	72	
Ln.	24/52	2.30	3.03	345	90	46	3.82	—	52	
Nn.	29/52	2.70	3.28	380	83	48	4.53	63	58	
Can.	29/52	1.5	1.54	185	74	23	2.49	—	31	

There is now a sufficient number of observations to predict with a fair degree of accuracy the basal metabolism of infants in various stages of malnutrition (Chart 1). These, however, have been compiled from observations made on numerous subjects showing various degrees of under-nutrition. We cannot find any observations made on an infant when well nourished, and then at different stages of emaciation. In one case of this series (the ruminator By.) it has, however, been possible to do the converse. The subject was a terribly emaciated infant 13 months old. It had its basal metabolism determined when it first came under observation, and again on two subsequent occasions while it was putting on weight rapidly and approaching the normal weight for its age. When the patient first came under observation it only weighed 3.75 kilos, while it.

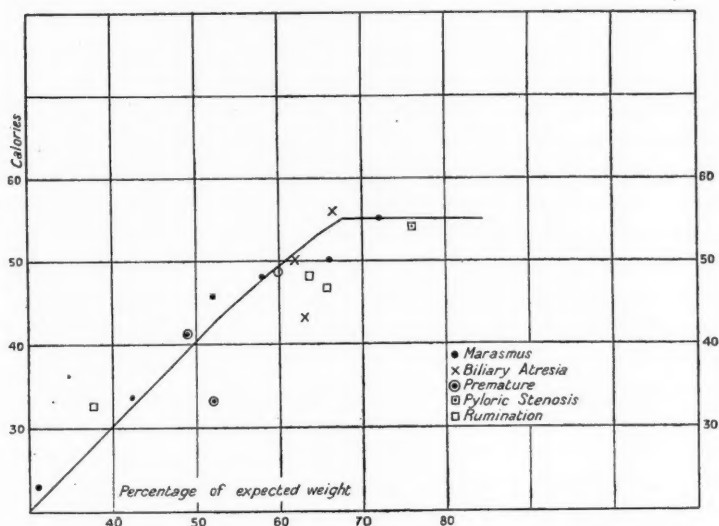


CHART 2. The heat output per kilo of expected weight and the state of nutrition (percentage of expected weight) in various wasting diseases.

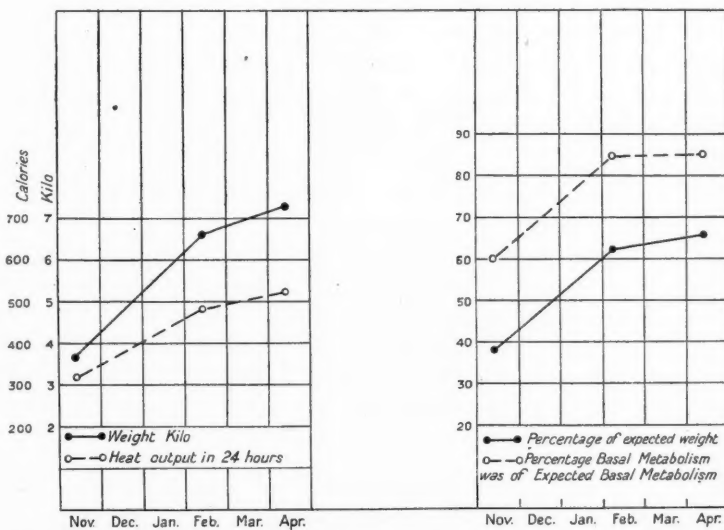


CHART 3. Showing the increase in the basal metabolism with the increase in weight.

CHART 4. Showing the approximation of the basal metabolism rate to normal as the state of nutrition improved.

should have weighed about 10 kilos, and its basal metabolism for 24 hours was only 320 Calories, while it should have been about 510 Calories. It put on weight very rapidly, so that after 3 months it weighed 6.30 kilos, and after 5 months 7.30 kilos. With the increase in weight the basal metabolism also rose, so that in April 1923, after five months' observation, its basal heat output was 520 Calories as compared to the normal for the age of about 600 Calories. Chart 3 shows the rise in the weight and basal metabolism as the child's condition improved. In Chart 4 we see the relative deficiency in weight and basal metabolism when compared to a normal child of the same age, and it will be observed that when the child's weight was about 60 per cent. below normal its basal metabolism was 40 per cent. below normal, but when its weight was between 30 per cent. and 40 per cent. below the normal for the age, its basal metabolism was only 15 per cent. lower than the normal for the age. This corresponds very closely with what had previously been found when studying different children at different stages of malnutrition, and here we have, at various stages in the course of this case of simple starvation, metabolic pictures identical with those presented by infants in various stages of atrophy pure and simple. It must be admitted, however, that when the child had arrived at a weight only one-third less than the expected weight for the age its basal metabolism was not as high as that of a normal child of that age, though, as previously stated, children who have only lost one-third of their weight should have a normal basal metabolic rate. In the present case, however, there is a certain difference. It had increased extraordinarily rapidly in weight, and probably the increase in active metabolic tissue (chiefly muscle) had not altogether kept pace with the increase in adipose and other metabolically inactive tissues, and therefore there was an undue proportion of inactive tissue. Furthermore, the child was older than those previously examined; it was 17 months old, and it is possible that its metabolism was more on a par with the metabolism of the adult, where there may be a decrease in the metabolism after only 6 per cent. of the body-weight has been lost. The difference, however, is not very great between the metabolic rate that was to be anticipated and what was actually observed.

The metabolic picture presented by this case and the cases of biliary atresia and pyloric stenosis corresponds closely with that produced experimentally in inanition, and, moreover, we know that there actually was inanition in these cases. The picture presented in marasmus is identical with these, so it seems reasonable to conclude that the disturbance of metabolism in marasmus is simply the result of inanition and not the cause.

Discussion of Results.

So far as our investigations have gone we have been unable to detect any gross abnormality in the absorption of food, nor in the oxidation of the food when absorbed, which will account for the condition. Unfortunately, it has not been

found possible to estimate the absorption of carbohydrate, but it seems possible that the key to the unravelling of part of the problem lies here. When we consider that all animals grow fat on carbohydrate, and that of all foods carbohydrate spares protein most efficiently, its importance cannot be overlooked. Clinically it is well known that excessive carbohydrate feeding is apt to lead to gastro-intestinal disturbance, and we are of opinion that this is one of the common causes of marasmus. It must be remembered that our investigations were made when there was no diarrhoea nor vomiting, but it is clear that when either of these is present there must be considerable loss of ingested food.

Although gastro-intestinal disturbance is one of the causes which may bring about marasmus, another is under-nutrition due to a diet deficient in quantity; we have found this to be extremely common in out-patient practice. On the other hand, in our hospital cases this factor was eliminated, and in practically all of these, when gastro-intestinal disturbance or one of the infections such as pneumonia was absent, there was manifest improvement.

Lastly, there are some cases (the disturbance of equilibrium of Finkelstein) where there is no gastro-intestinal disturbance, where an adequate diet is given, and yet which do not thrive. In our opinion these cases are rare, and unfortunately we have never had an opportunity of examining the metabolism in an undoubted example of this condition. We must conclude, therefore, that marasmus is a condition brought about by inanition, and that in the vast majority of cases this inanition is caused by an insufficient diet or by gastro-intestinal disturbance.

Conclusions.

1. In the absence of gastro-intestinal disturbance, there is no evidence of defective absorption or abnormal utilization of food in marasmus.
2. The metabolic picture in marasmus is identical with that of under-nutrition whatever the cause.

We have much pleasure in recording our thanks to Dr. Leonard Findlay, who kindly gave facilities for the examination of the cases, to Prof. Cathcart for much helpful criticism, and to the Medical Research Council, who defrayed the expenses of the work.

APPENDIX.

Methods.

1. *Estimation of fat in the stools.* Neutral fat and free fatty acids were extracted from the dried stools with ether and weighed. The free fatty acids were estimated by dissolving them in neutral alcohol and titrating with N/10 NaOH; they are expressed as stearic acid. Neutral fat was estimated by difference. Insoluble soaps were converted to free fatty acids with HCl, and extracted with ether and weighed.

2. *The fat in the milk* was estimated by the Warner-Schmidt method.

3. *The nitrogen in the urine, stools, and milk* was determined by the Kjeldahl method.

4. *The caloric value of the stools.* The Berthelot-Mahler bomb calorimeter was used to determine this.

5. *The collection of the faeces and urine.* A special metabolism bed was used. The method is described by Telfer (18).

6. *The method of determining the respiratory exchange.* The method described by Benedict and Talbot (3) was used. The apparatus is a closed circuit system, and both the oxygen used and CO₂ expired are estimated. The duration of the experiments is only limited by the dietary and hygienic requirements of the subject. The experiments described in this paper lasted between 30 and 40 minutes, usually 40 minutes, and were always preceded by a preliminary period of about 30 minutes, during which the temperature within the apparatus became fairly constant and the subjects became quiet, indeed they frequently went to sleep. The movements of the subject in the apparatus were recorded on a kymograph; the method used has been described in a previous paper (5). Only experiments where the subject was asleep or the movements were slight were considered to give basal findings. The accuracy of the apparatus was frequently tested by doing an experiment with a small burning alcohol lamp substituted for a subject and estimating the ratio of oxygen used to the CO₂ given off. The theoretical $\frac{\text{CO}_2}{\text{O}_2}$ ratio for the combustion of alcohol is 0.66; if results below 0.64 or above 0.68 were obtained, the apparatus was considered defective and was not used for an experiment until it had been overhauled and a satisfactory alcohol test obtained. The subjects were on a diet of cow's milk, to which sugar was added in some cases. They were fed immediately before the commencement of the preliminary period—that is, about 40 to 60 minutes before an experiment proper began.

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CONGENITAL PANCREATIC DISEASE WITH INFANTILISM

By CECIL CLARKE AND GEOFFREY HADFIELD

With Plates 21 and 22

Introduction.

A CHILD of four was admitted to the General Hospital, Bristol, under the care of one of us (C. C.) during December 1921, suffering from fatty diarrhoea dating from birth. She was under-sized and under weight, passed large, bulky, unformed, and obviously fatty stools, but had never been jaundiced; the liver was greatly enlarged. Death from an intercurrent infection took place seven weeks later. The post-mortem examination confirmed a presumptive diagnosis of pancreatic disease, showing an extensive atrophy of the pancreas without obvious primary cause; the liver was extremely fatty and the colon dilated and thickened.

The case seems to us to merit publication quite apart from the rarity of pancreatic disease in children. Several points in the history and physical condition suggested a diagnosis of coeliac disease, in itself an obscure complaint; this diagnosis, untenable on closer clinical observation, was definitely excluded by the post-mortem examination. Although the pancreas showed changes of an unusual type and degree of severity, glycosuria was absent; finally, the histology of the pancreas yielded a striking but indirect confirmation of modern experimental and clinical knowledge of the function of the pancreatic islet tissue.

Case Report.

E. H., a girl aged 4 years and 4 months, was first seen in the Out-patient Department of the General Hospital, Bristol, on 21.11.21. The history obtained from the mother was so definite that a provisional diagnosis of 'pancreatic diarrhoea' was made and the child recommended for admission. She was admitted on 3.12.21, transferred to the Ham Green Isolation Hospital, Bristol, for diphtheria on 20.1.22, dying from broncho-pneumonia nine days later.

Previous history. Measles at nine weeks. No illness other than that complained of.

Family history. There had been eight pregnancies, as follows:

1. Healthy child, aged 16, strong and well.
2. Still-born at full term, breech presentation, and difficult labour.

(Q.J. M., July, 1924.)

3. Healthy at birth, died at $2\frac{1}{2}$ months from pneumonia; case-notes stated that this was a healthy child.

4. Still-born, labour normal at full term. Child large and well developed. Died from asphyxia neonatorum.

5. Healthy at birth, lived $2\frac{1}{2}$ months. Normal labour at full term. Well-developed child. Died of broncho-pneumonia following whooping-cough.

6. Healthy boy, aged 10, strong and well.

7. *Patient born 4.8.17.*

8. Healthy girl, aged $2\frac{1}{2}$ years, strong and well. Mother, aged 36 at the birth of this child, a charwoman; never confined to bed except for pregnancies: worked up to three weeks before the birth of the patient. Father, ten years older than wife: a healthy man, never ill in bed, a tractor driver; the parents were not related. The Wassermann reaction of both parents was negative.

Patient weighed $8\frac{3}{4}$ lb. at birth. Mother in excellent health during gestation, labour normal. Child was breast-fed until eighth month, then given bread and potato, until finally weaned altogether at tenth month. Quite soon after birth, when child was a 'tiny baby', the mother noticed that the number of stools was considerably more than with her other children, and that they were very offensive and greasy. The napkins were difficult to clean, required a 'lot of soap', and the motion had to be 'scrubbed out' of them. She did not remember the child having a normal stool; the motions were always large. At about the age of 5 to 6 months, motions became more greasy, and often left a stain in the napkin like 'thin candle grease'. The mother was not greatly perturbed about this abnormality, as the child thrived, took the breast eagerly, never ailed, and slept well. When the child was about 9 months old, a neighbour alarmed the mother by suspecting that the 'diarrhoea' and offensive motions were due to 'consumption of the bowels'. The child was taken to hospital, and in view of the fact that the case attracted no attention during a long attendance, the real condition cannot then have been suspected.

The mother's observations from this point onwards were more critical, although no great change seems to have taken place in the child's condition. After weaning, the child's appetite was enormous: she was continually craving for food, and was very fond of meat. The stools became huge, were much more greasy, always pale, and very offensive; they numbered about nine during the twenty-four hours. At no time did the mother remember a formed stool being passed; she had to make napkins four times the usual size to accommodate the motion. The call to stool was occasionally so urgent that it became necessary to 'scrape up' the motion from the floor—it was impossible to 'wash it off'. Towards the end of the second year the motion was occasionally greenish and slimy. At no time were there acute abdominal symptoms or jaundice. Child did not walk until the age of two, she talked before she walked, became and remained very quick-witted, amusing, and old-fashioned. During the second year she put on very little weight, and grew slowly. After walking, she fattened for a few months, but the stool remained the same and the appetite voracious: she refused

milk and slops, jam and sweets, but consumed large amounts of potato and was very fond of meat and cheese. She now began to complain frequently of tiredness, and was observed to be getting thinner. The fatty diarrhoea and large appetite remained as during the second year, and at about the age of $2\frac{1}{2}$ the mother noticed the abdomen was very prominent; six months before admission to hospital the diarrhoea had become worse and was now 'a great trial' to the mother; also the child was losing weight and becoming more frail, yet she complained very little. She did not appear to have had increased thirst or polyuria. Wasting was rapid three months before admission to hospital—the highest weight recorded, 30 lb., was at the age of $3\frac{1}{2}$ ($25\frac{1}{2}$ lb. on admission, nine months later).

Condition on admission. Age, $4\frac{4}{12}$ years. Weight, $25\frac{1}{2}$ lb. Height, 35 inches.

The child looked about two years old, was pale, seemed tired, and disinclined to talk. Extremities cold and general nutrition poor. Tongue clean but dry. Teeth complete, naturally erupted. Pulse, average 100. Afebrile. Chest normal. The abdomen was evenly distended, but not tympanitic; vague general discomfort on palpation, especially on left side. The firm liver edge was easily palpable 1 in. below the umbilicus in the mid-clavicular line, the surface smooth, and the organ did not feel hard. Tip of spleen felt. Urine, 1,016. Albumin and sugar absent. Rothera's test for acetone negative.

Stools, average 5 in twenty-four hours, varying from 3 to 8. Each stool large (average bulk 6 oz.), greyish-white with a faint brown tinge, and very offensive. On the surface, many large semi-fluid fatty drops, and many fatty drops floating in the fluid about the stool. The stools were not like 'greasy porridge', nor any other article of diet with which we are acquainted. Microscopically—chiefly fat globules, no fatty acid crystals or soap flakes. No pathogenic organisms isolated by plate culture.

Progress. The weight remained stationary. No sugar was found in the urine on at least eight occasions, nor was Rothera's test ever positive. On an almost fat-free diet the stool did not alter in character, although the number of stools fell to 5 per day. On 16.1.22 a strict fat-free diet was given with no change in the character of the stool. The child much preferred an ordinary mixed diet with plenty of meat, and this was allowed after January 12. Neither diet nor drugs produced any alteration in the physical state, and the frequency of the motions again averaged 4 to 8. Tablogestin, half a tablet t.d.s., was given from December 22 to January 16 without appreciable effect; pancreatic extracts alone were not tried, but by January 20 the general condition was so poor that all active remedial treatment was abandoned.

23.12.21. Temperature 100° F. Left-sided otorrhoea.

12.1.22. Otorrhoea on both sides.

14.1.22. Continued fever, 102° – 101° F. Pulse 130–140, with nasopharyngeal discharge. *B. diphtheriae* found in discharge. Transferred to Ham Green Isolation Hospital.

29.1.22. Death from broncho-pneumonia.

Post-mortem examination. Performed 30.1.22, twelve hours after death.

Externally. Moderate oedema of hands, forearms, and feet, pitting with difficulty. Wasting of head and neck; thorax poorly covered and abdomen prominent. *Tongue*, normal. *Oesophagus*, normal. *Tonsil*, cheesy exudate in several crypts. *Pharynx*, normal. *Larynx*, mucous membrane reddened but intact. *Thyroid*, normal. *Deep cervical glands*, slightly enlarged and congested. *Trachea*, contained much thin muco-pus. *Thorax.* *Lung (right)*, a raised purple nodule $1\frac{1}{4}$ inches in diameter on the posterior surface of the right middle lobe, honeycombed by small abscess cavities with recent ulcerative walls; basal oedema. *Lung (left)*, pus could be expressed from the larger bronchi of the lower lobe; upper lobe very oedematous. *Hilus and tracheal glands*, enlarged, reddened, and firm. *Heart*, slight myocardial pallor only. *Aorta*, normal. *Abdomen*, clear fluid in small quantity. *Liver*, considerably enlarged; descending colon prominent and dilated. Noteworthy diminution of fat in mesentery and great omentum. *Stomach*, normal. *Small bowel*, normal, no abnormality in Peyer's patches, wall of normal thickness. Lymphatic glands of mesentery and gastro-hepatic omentum, enlarged, reddened, and firm. Ampulla of Vater, normal. *Large intestine*, although almost empty, stood out prominently, occupying a considerable space in the left flank and pelvis. Its walls felt rigid and leathery throughout, especially from the splenic flexure downwards. The wall of the caecum and ascending colon was thickened, from 2.5 to 3 mm., the mucous membrane reddened but not ulcerated. This thickening of the colon, still more evident in the transverse colon, attained its maximum in the descending colon; this portion was more rigidly dilated than the rest of the large bowel, and five inches above the commencement of the iliac colon there was an area of ulceration, oval in shape (1.2 by 3 cm.), running in the long axis of the bowel. The edge of the ulcer was irregular and felt rather hard; the muscularis mucosae formed the floor, covered by flat reddish granulations; its peritoneal surface was normal. The wall of the bowel for 6 cm. above and below the ulcer was 3 to 3.5 mm. thick, the mucous membrane was injected and showed an occasional haemorrhagic point. After hardening in formalin, the thickening of the wall was seen to be due to an increase in thickness of the submucous coat, easily recognized in the hardened specimen as a thick reddish-white line; eight other smaller foci of ulceration were found in the descending colon.

Liver. Considerably enlarged, the lower edge in the umbilical plane. Weight, 1,247 grm., 2 lb. 12 oz. The organ was uniformly lemon-yellow in colour, and devoid of normal lobular pattern. The cut surface was flat, bloodless, and very greasy; a scraping marked paper and covered the blade of a warmed knife with oil drops. The liver substance was friable. Perl's reaction for iron and the iodine reaction for amyloid were negative. The organ floated on water with about nineteen-twentieths of its volume submerged. The gall-bladder contained viscid deeply-pigmented bile which flowed easily along the common duct. No abnormality found in the extra-hepatic biliary system. The glands of the portal fissure were moderately enlarged.

Pancreas. A shrunken-looking, dead-white, fatty mass occupied the position

of the pancreas, in appearance quite unlike the normal gland. It only partly filled the duodenal loop, and was irregularly and deeply constricted at several points along its length. It showed no trace of a lobular pattern on the surface, and was not adherent to surrounding structures (weight, 14.4 gm.; length, 6.5 cm.; greatest antero-posterior diameter, 1.8 cm.) [Weight of normal pancreas, between 5 and 7 years, varies between 20 and 40 gm. (Hutinel and Nobecourt), and at 4th year, 18 to 20 gm. (Rössle).]

The cut surface was flat and bloodless, the consistence firm but not tough, and the colour dead white, except for three or four light brownish-red, roughly circular areas, each 0.5 to 0.75 mm. in diameter, lying in the central portion of the gland. Under a lens these central areas were found to be small groups of lobules lying around the duct. They formed a central strand of surviving pancreatic tissue running through the organ from head to tail. After hardening, a series of sections were made at intervals of about a centimetre along the gland; the central duct was seen in all sections, and showed no naked-eye dilatation, constriction, or calculus.

Kidneys. The cortex was pale and swollen, and the cortical pattern obscured. The capsule stripped easily, leaving a smooth surface.

Suprarenal (left), deep red in colour and oozed blood on section. No suggestion of gross suprarenal haemorrhage. The pattern of both glands was retained on section.

Retroperitoneal glands showed slight enlargement. The pelvic organs were normal.

The brain and cord were not examined.

Histopathology. Pancreas. The organ was fixed and hardened in formol-saline; owing partly to this, but probably much more to post-mortem autolysis, the finer cytology of the tissue was lost, and staining by specific methods—e. g. by Bensley's stain—unsuccessful.

Sections were taken about the junction of the head and body of the gland. The thin strand of pancreatic tissue described under the naked-eye examination was made up of ten gland lobules, the remains of three other lobules, and two large ducts: it was closely invested by dense mature fibrous tissue which, with the contained lobules and ducts, was embedded in fat, carrying nothing more than a few vessels, and small isolated groups of cells. More than half the portion constituting the pancreatic remnant was composed of fibrous tissue: the central strand occupied about one-eighth of the whole sectional area, and this was much smaller than normal. To state that the pancreas contained one-twentieth of the normal amount of secretory gland would be to give a generous estimate.

The moderate degree of post-mortem autolysis present was not severe enough to destroy many of the finer histological details: it did, however, obscure the high-power histology of the islets of Langerhans, but permitted of the recognition of these structures.

In the dense fibrous tissue investing the lobules clear evidence of active inflammation was lacking, as also in the centres of the lobules. The tissue was

remarkably bloodless. There was a moderate degree of interacinous fibrosis, but no evidence of cell-infiltration between the tubules; the cells of the acini appeared pressed together and were not well defined; the lumen was preserved in most acini, except here and there where the fibrosis had almost destroyed a whole lobule and a few shrunken acini alone remained. In several lobules the cells of the islets of Langerhans could be made out easily, and, compared with normal post-mortem material fixed at a similar interval after death, did not show any pathological change. As a rule, the lobular duct-system was normal, except that the lumen of the large ducts was filled by desquamated epithelium: yet there was no inflammatory change present in the duct-wall or in its immediate neighbourhood to account for this; the ducts were not dilated, and this desquamation was probably a post-mortem change.

Scattered throughout the fibrous tissue enclosing the surviving lobules were several groups of mononuclear cells; they formed circular, discrete, and very cellular foci one-eighth to one-quarter the diameter of the larger lobules. No active inflammatory change was seen near them, and the cells were of the size and shape of those in the lobular cell islets. Many similar collections of these cells were found lying free in the fat at some distance from the central strand of tissue. These cell collections were doubtless cell islets, but an attempt to demonstrate granules in these cells by Bensley's method was unsuccessful; this is usual in all but fresh pancreatic tissue. These islets numbered 1.76 to the square mm., and their average diameter was $114\ \mu$. [The normal islets measure from $100\ \mu$ to $400\ \mu$; islets larger than $400\ \mu$ are very rare (Opie). The average number of islets varied considerably, but they were always most numerous in the tail. Laguesse found the number in the body somewhat less than one islet per sq. mm., Sauerbeck found one islet per sq. mm., Dewitt 1.5 per sq. mm., Opie 0.9 per sq. mm. in the head and body.]

There was therefore more islet tissue per unit surface than is present in the body of the normal adult gland.

Liver. Each lobule was represented by a mass of closely-packed fat globules staining uniformly with Scharlach R. The lobular pattern was faintly indicated by the interlobular connective tissue network, which was more cellular than normal, and stood out rather prominently from the fatty parenchyma. A great majority of the cells of the lobules were distended by a single fat droplet with the cell nucleus excentric. At the edges of the lobules were a few unaltered hepatic cells. The blood and bile capillaries of the lobule were normal. The cell increase in the interlobular network and in the portal canals was made up of lymphocytic cells and spindle-shaped fibroblasts, with a few polynuclear leucocytes which had infiltrated the edges of some of the lobules. Cell infiltration of the parenchyma was neither constant nor conspicuous. In the portal canals a moderate degree of proliferation of the bile-ducts had occurred, a change much less prominent in the interlobular tissue. The organ, as a whole, was anaemic and the changes in the supporting tissue not pronounced.

Large intestine. In all sections examined at various levels there was very

definite inflammatory thickening of the submucosa, which showed increased vascularity, and in its deeper layers well-established fibrosis. Ulceration was found only in the descending colon, from a point three inches below the splenic flexure to the rectum. The cell exudate in the submucosa was lymphocytic, perivascular, and of a chronic nature. The ulceration was of no specific character; the ulcers themselves showed superficial infection and necrosis.

Small intestine. Sections at various levels showed no evidence of disease.

Summary of Post-mortem Findings.

1. *Atrophy of the pancreas.* The gland was represented by fat and a fraction of normal gland tissue estimated at one-twentieth. The surviving pancreatic tissue was active, but appeared to be undergoing slow replacement fibrosis; it contained islet tissue in more than the normal amount; there was no clear evidence of pancreatitis.

2. *Fatty metamorphosis of the liver* unaccompanied by any sign of hepatic necrosis, clear-cut cholangitis, or pylephlebitis.

3. *Chronic colitis*, with superficial ulceration in the descending colon only.

Summary of Case Report.

A girl, aged 4 years and 4 months at the time of her death, had suffered from fatty diarrhoea certainly from the fifth month, and had, in all probability from birth, passed stools containing an excess of fat. Her facial appearance and weight was that of a child of two, her height that of a child of three. The abdomen was distended, in part due to a considerable enlargement of the liver. The urine was normal. The stools averaged five per diem, were unformed, voluminous, and pale; drops of fat were visible by the naked eye on the surface, and microscopically there were many fatty droplets but no fatty acid crystals. No improvement took place on a strict fat-free diet. She died of broncho-pneumonia following nasal diphtheria. Lying in the position of the pancreas was a shrunken-looking mass of fat, running through which was a thin strand of gland-tissue containing many cell-islets. The liver showed high-grade fatty infiltration; the colon, chronic thickening and some ulceration.

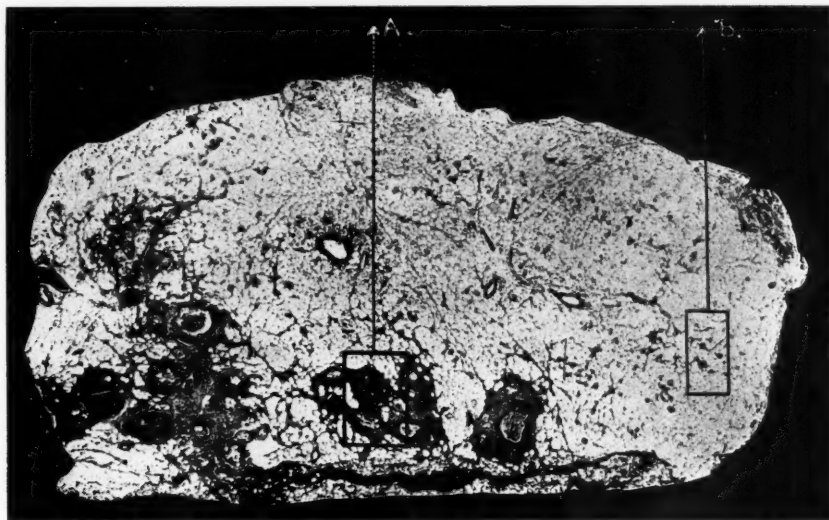


FIG. 1

FIG. 1. Photograph of a complete transverse section of the pancreas at the junction of the head with the body of the gland. Magnification, 9 diameters.

The wide expanse of fat is seen in which lies the strand of surviving pancreatic tissue.

The gland tissue included in the rectangle A is seen under higher magnification in Figs. 2 and 2a: the structure of the fatty tissue included in the rectangle B, in Figs. 3 and 3a.

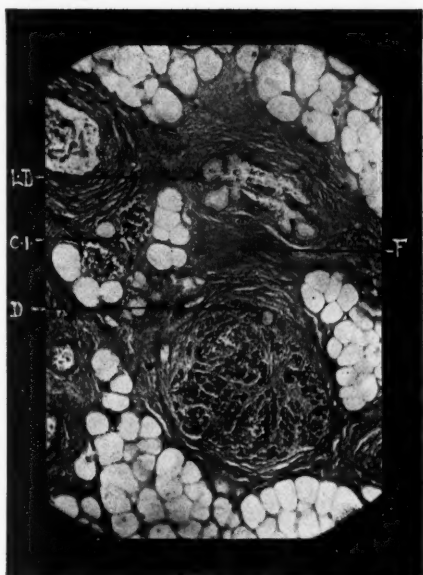


FIG. 2

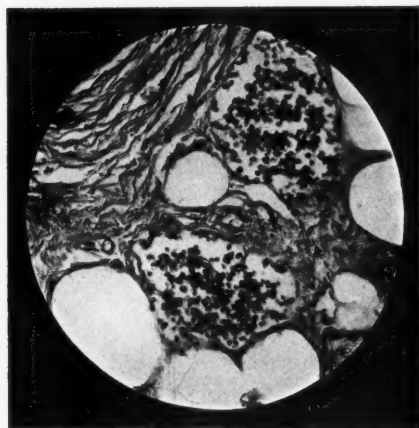


FIG. 2a

FIGS. 2 and 2a. Photographs showing the structure of the surviving pancreatic tissue. The area included in the rectangle A in Fig. 1.

FIG. 2. Low-power view. A lobule is seen embedded in mature fibrous tissue (F). D, a normal lobular duct. LD, a dividing interlobular duct. C.I., two isolated masses of islet-tissue.

FIG. 2a. The isolated cell-islets seen at C.I. in Fig. 2 under higher power.

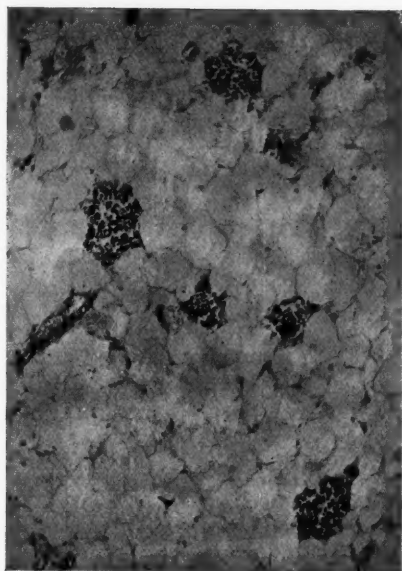


FIG. 3

FIG. 3. Photograph of the area included in the rectangle B in Fig. 1.
Low-power view of the fat containing several masses of islet-tissue.

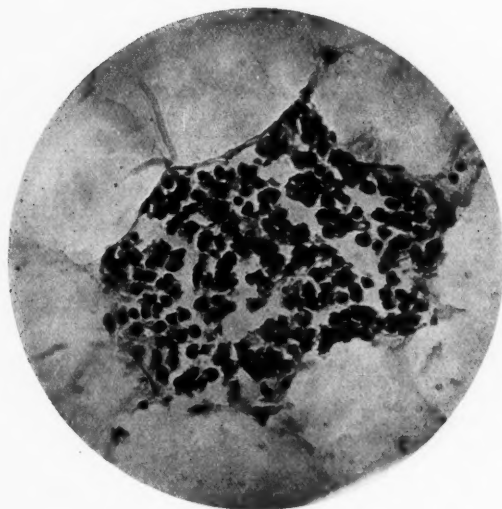
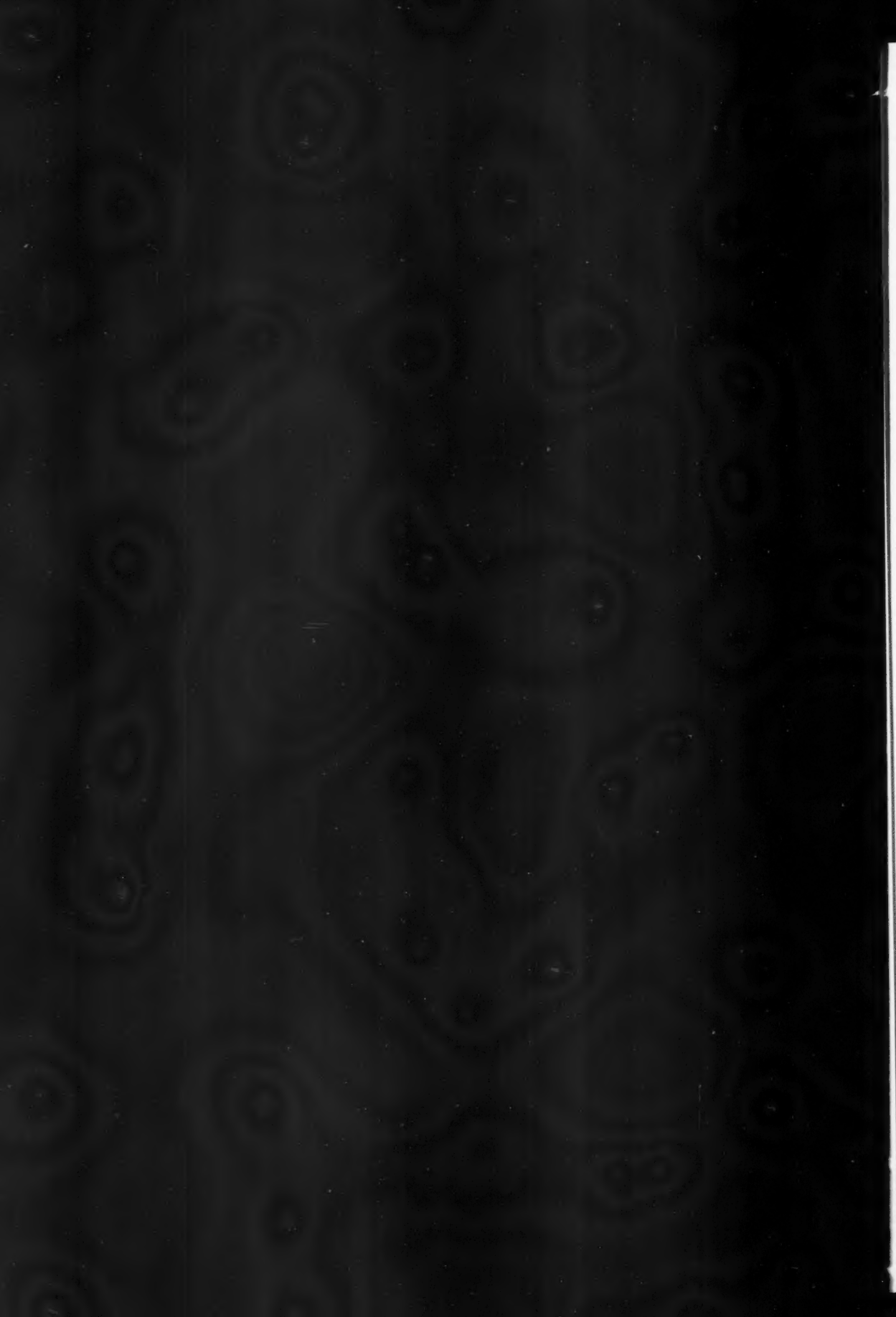


FIG. 3a

FIG. 3a. High-power view of one of these cell-islets.

FIGS. 3 and 3a show the appearance of the islet-tissue lying
free in the fat which surrounds the gland-remnant.



TULARAEMIA IN MAN FROM LABORATORY INFECTION

BY J. C. G. LEDINGHAM AND F. R. FRASER

With Plates 23 and 24

PART I. INTRODUCTION AND CLINICAL FEATURES.

Introduction.

TULARAEMIA is a general infection due to *Bacterium tularense*, and has hitherto been confined to North America, where it causes a plague-like disease in rodents, and has given rise to several cases of infection in man. Three cases have recently occurred in this country, the infection arising in laboratory workers who were investigating the organism at the Lister Institute.

In 1911 McCoy (15) was examining ground squirrels in California for evidence of plague infection, and discovered in the course of this work a plague-like disease that was not due to *Bacillus pestis*. In 1912 McCoy and Chapin (16) isolated the specific organism from the blood, and it was named after Tulare County, California, where the epidemic in the ground squirrels was being investigated. Since then the organism has been found in jack rabbits, 'cotton-tail' rabbits, and two species of squirrel; and foci of infection have been recognized in California, Utah, Wyoming, Idaho, Colorado, Indiana, Ohio, Tennessee, North Carolina, and Washington (D.C.).

The organism is readily isolated from the blood of infected animals, and it is probable that the infection is conveyed to them by blood-sucking insects (see Part II).

Probably the first human cases to be described were reported in 1910 by R. A. Pearse, who read a paper before the Utah State Medical Association, referring to three cases seen in 1908 and three in 1910 of fever and malaise following insect bites (5). The site of the bite became inflamed and ulcerated, and there was marked swelling of the regional lymphatic glands. The incubation period varied from two to five days, the duration of the disease from one to four weeks, and the severity from slight malaise to death. The subsequent work of E. Francis on cases proved bacteriologically makes it certain that the cases described by Pearse were due to infection with *B. tularense*.

The first instance of infection in man to receive bacteriological proof was reported in 1914 by Wherry and Lamb (20), who isolated *B. tularense* by means of guinea-pig inoculation from the scrapings from the ulcers in a severe case of

[Q. J. M., July, 1924.]

conjunctivitis. The clinical features were described by Vail (18), who reported that, in addition to unilateral ulcerative conjunctivitis, there was fever, prostration, and painful swelling of the regional lymphatic glands. A second similar case was reported by Wherry (19) and Sattler (17).

In 1919 Francis (1) reported that a fatal case of what was called 'deer-fly' fever was due to infection with *B. tularensis*, and in 1921 he reported (2) six non-fatal cases, all from the State of Utah. These cases occurred in the summer months, and following an insect bite developed a painful swelling of the regional lymphatic glands. On the third day after the bite, or later, a black necrosing ulcer developed at the site of the bite. This suppurated and sloughed, leaving a punched-out ulcer. In all seven cases suppuration occurred in the regional lymphatic glands, and they had to be incised. The fever was characterized by daily remissions, and the majority of the patients did not recover fully for two or three months. 'Two patients', Francis reports, 'spent the first month in bed, the second month about the house, and the third month doing light work.' The prostration during the acute stage, and the pronounced general weakness during the slow convalescence, rendered the condition a serious one to farm-workers during the busy season of the year.

In 1922 Lake and Francis (10) reported that all six men who had been closely connected with the laboratory investigations on *B. tularensis* in the United States Public Health Service during the two previous years had contracted the disease. Two contracted it while working in a field laboratory in Utah, and four at the Hygienic Laboratory at Washington. All were highly skilled workers, with long experience in the handling of infectious material, and were employed in handling or dissecting animals infected with *B. tularensis*. In contrast with the cases acquiring the disease in the field, in none of the six laboratory workers was there any evidence of insect bite, nor any lesion or involvement of lymphatic glands. In each case there was a sudden onset, with high temperature, which, after subsiding almost to normal about the third day, again became high and gradually fell to normal at the end of about three weeks. Convalescence was slow, extending over two months. One patient developed a second attack, associated with a papule on the finger and enlarged and painful regional lymphatic glands, two years and five months after the first attack, while other three of the men returned to the same work without developing further attacks. In three of the cases, attempts were made to isolate the organism from the blood, but they were unsuccessful. The diagnosis of the laboratory cases rested on the exposure to infection, the three weeks' fever, the absence of signs significant of other known infections, and the positive agglutination reactions and complement fixations obtained with the sera of all six patients. In two of the cases occurring in Utah the organism had been isolated from the blood, but in both of them the disease was much more severe than in any of the laboratory cases, and in one there was a fatal termination.

In 1923 Francis reported (6) a case of tularemia in a man who sold rabbits in the Washington market, and on examination of a number of rabbits offered

there for sale, found seven that were infected with *B. tularensis*. In this case there was a localized glandular enlargement and a history of a sore on one finger.

Reports of Cases.

In each of the three cases to be reported here, the patient was working in the laboratory with cultures of *B. tularensis*, and was handling infected animals and dissecting animals that had died from infection with the organism. In Cases 'B' and 'R' the patients had been working with the organism for three to five months before becoming ill, but in Case 'S' the patient had only worked with the infected animals on one occasion, having come from another department when the regular workers (Cases 'B' and 'R') became ill. All three were highly trained and had had extensive experience in the handling of infected material. Another member of the staff of the Institute had also worked with the infected material over a period of some months without acquiring the disease, and a laboratory attendant who had charge of the animals also handled the infected animals and the carcasses, but did not show any signs of infection.

For much of the details in the case reports we are indebted to the patients themselves, and to Dr. Charles Corben we are indebted for permission to investigate Case 'B'.

Case 'B'. Male, aged 38 years.

Previous history. Had typhoid and scarlet fever in childhood, and influenza in 1918. Otherwise had had no serious illnesses, but was never robust, suffering from frequent headaches that caused him to miss a day's work from time to time.

Onset and course. Aug. 31, 1922. Complained of aching all over, of malaise, of generalized headache, and of pains in the bones of a vague constant aching character. The calves were tender to the pressure of the bed, and the throat felt 'relaxed'. The temperature was 100° F., where it remained for the next two days, while the symptoms continued as before. In the next few days he felt better but very weak, and returned to work on Sept. 11, but did not put in more than a few hours each day.

Sept. 15, 1922. While at work initial symptoms returned, and on reaching home had a mild rigor. Temperature 100° F.

Sept. 17, 1922. Temperature 103° F., highest record during illness (see Chart I). Appetite poor, mouth dry. Slept restlessly, as if feverish. Aching and tenderness as before.

Sept. 18, 1922. Blood taken for culture and agglutination reactions for typhoid and paratyphoid: all negative.

Sept. 22, 1922. On examination: Lay on back, but turning restlessly from time to time to relieve aching. Looked exhausted, but was mentally alert. Face slightly flushed. Skin moist and warm. No sores or inflamed areas on fingers, &c. No tenderness on handling limbs or on deep pressure. No enlargement of lymphatic glands discovered, except that epitrochlears were palpable. Breath had a heavy odour, but not foul. Tongue clean. Temperature 101° F. Pulse 72, quick in character. Blood-pressure 150-85. Respirations quiet and natural. Cardiac impulse was forcible, the first sound feeble at the apex, and there was a soft systolic murmur audible in all areas. A few rhonchi were heard in right interscapular space, otherwise lungs natural. No enlargement of spleen; abdomen and nervous system natural.

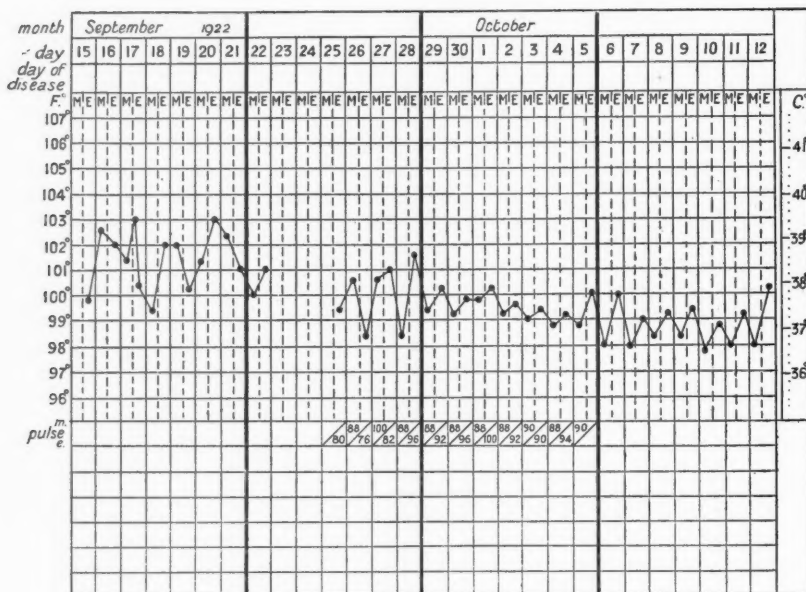


CHART I.

Case 'B'. Records of temperature accompanying second attack of fever (probable onset of tularaemia), and records of pulse-rate while in hospital.

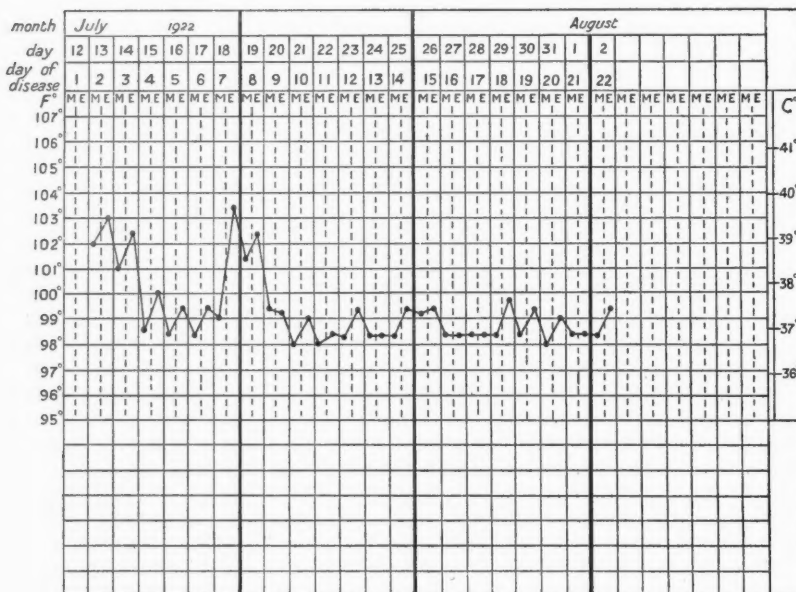


CHART II.

Case 'R'. Temperature chart showing onset of fever and secondary rise.

TULARAEMIA IN MAN FROM LABORATORY INFECTION 369

Blood count: R.B.C.	4,970,000 per c.c.
Hb.	85 per cent.
W.B.C.	4,600 per c.c.
Polymorphs	3,680 " "
Lymphocytes	600 " "
Large monos.	230 " "
Eosinophils	50 " "
Basophils	50 " "

Agglutinations. Negative for *B. typhosus* and *B. paratyphosus A* and *B.*

Blood cultures. Negative in aerobic and anaerobic broth, and in Noguchi medium. Guinea-pig inoculated with citrated blood remained healthy.

Sept. 25, 1922. Admitted to hospital. On examination, same as on 22.9.22. Urine contained slight trace of albumin. For temperature and pulse-rates see Chart I.

Sept. 28, 1922. Temperature 101.6°.

W.B.C.	8,800 per c.c.
Polymorphs	7,100 " "
Lymphocytes	1,500 " "
Large monos.	100 " "
Eosinophils	100 " "

Sept. 29, 1922. Urine culture negative. Stool culture showed no non-lactose fermenters. Agglutination negative for two strains of *B. melitensis* and two strains of *B. paramelitensis*.

Oct. 2, 1922. Agglutination with *B. tularensis*—definitely positive (for details see Part II).

Oct. 4, 1922. Temperature settling.

On examination, systolic murmur was not heard. There was a small gland palpable and slightly tender behind angle of jaw on left side.

Oct. 5, 1922. W.B.C.	8,800 per c.c.
Polymorphs	5,400 " "
Lymphocytes	3,100 " "
Large monos.	130 " "
Eosinophils	50 " "
Basophils	90 " "

Returned home, continued at rest in bed. During Nov. 1922 the fever disappeared and a slow convalescence commenced, interrupted from time to time by mild attacks of aching on both sides of the neck with slightly tender palpable cervical glands. At the end of Dec. 1922, and at the end of Jan. 1923, had returns of feverishness with aching in neck and back for four or five days. Continued to be easily tired and appetite remained poor.

Feb. 14, 1923. On examination, temperature 98.4° F. Pulse 64. Respirations 20. Looked brighter and more alert than when in hospital, but still had tired appearance. No abnormal physical signs detected. Many acne lesions on back of thorax, which he said had developed during his illness. He had never been troubled with this previously.

Blood count. R.B.C.	5,600,000 per c.c.
W.B.C.	10,800 " "
Polymorphs	6,780 " "
Lymphocytes	3,530 " "
Large monos.	110 " "
Eosinophils	330 " "
Basophils	50 " "

Returned to work.

Mar. 7, 1923. Reported able to carry on his work, but still having occasional attacks of swollen and tender cervical lymphatic glands and slight rises of temperature.

Dec. 1923. Reported gaining strength, and now practically as before infection, but still occasional attacks of tender cervical glands.

Case 'R'. Female, aged 34.

Previous history. Measles in childhood. Influenza in 1919. Up to age of 7 years had frequent attacks of acute arthritis, and had occasional joint pains since. Is athletic, plays much tennis and goes for long walks. Never found work in laboratory hard.

Onset and course.

July 12, 1922. In evening felt weak and chilly, and while travelling home in the train had a mild rigor. Temperature was not taken, but she took no dinner as she felt nauseated.

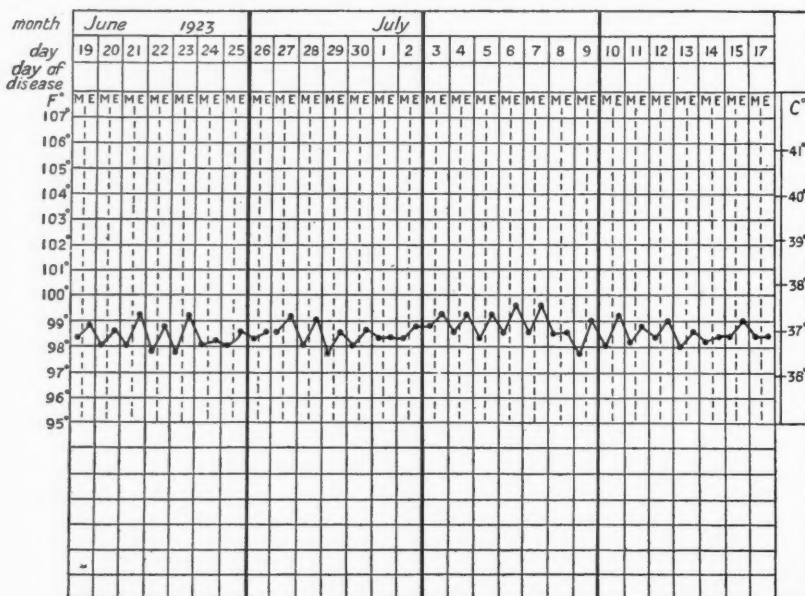


CHART III.

Case 'R'. Temperature chart showing irregular periods of fever one year after onset.

July 13, 1922. Fainted on attempting to get up. Temperature 102° F., and later in the evening 103° F. (see Chart II). Stayed in bed for four days, feeling slightly nauseated, and had extreme weakness and a disinclination to do anything. On the seventh day from the onset she was feeling better and got up. In the evening the temperature was 103.4° F., and she remained in bed for the next four days, when the temperature again settled and she felt slightly better. Following this the evening temperature was frequently above normal, and she felt weak and tired, but she noticed that after three or four days of increased weakness there would be a few days when she felt better, before the weakness returned for another period of three or four days. This continued during a visit to the sea-side for five weeks.

July 26, 1922. Agglutination with *B. tularensis*—definitely positive (see Part II).

TULARAEMIA IN MAN FROM LABORATORY INFECTION 371

Sept. 1922. Returned to work, and immediately had a relapse, similar in character to the onset, but the temperature did not settle so quickly, and in addition to the malaise and general weakness there was great mental depression. At the end of three weeks the condition returned to that existing before the relapse—three- or four-day periods of low fever accompanied by exacerbations of the weakness and depression, separated by increasing intervals.

Dec. 1922. Noticed that the glands in the neck were enlarged and tender, and that there was at times an aching feeling behind the angles of the jaws. Towards the end of Jan. 1923 she returned to work, but found she was very easily tired and that the bouts of fever with mental depression and aching in the neck were more obvious.

Feb. 14, 1923. On examination, patient was a well-developed woman who showed no signs of emaciation. She was bright and alert and of good colour, but by the end of the examination appeared tired, depressed, and pale. Temperature 99.6° F. Pulse 100. Respirations quiet and natural. A few small lymphatic glands were palpable anterior to the sterno-mastoid on both sides, but larger on the left side, and there was slight tenderness behind the angle of the jaw on the left side. No glands were palpable in the groins or axillae, but there was slight tenderness in both axillae. The tongue was dry and slightly furred all over, the teeth in good order, and the tonsils were visible but not inflamed and appeared healthy. There was a soft systolic murmur at the apex, and also at the pulmonary area, but otherwise the circulatory, pulmonary, digestive, and nervous systems appeared normal. The spleen was not palpable. There were many acne lesions on the back of the thorax, which had developed during the illness. She stated that she was never troubled by them previously.

<i>Blood count.</i>	R.B.C.	4,600,000	per c.c.
	Hb.	65	per cent.
	C.I.	0.7	
	W.B.C.	12,400	per c.c.
	Polymorphs	10,000	" "
	Lymphocytes	2,100	" "
	Eosinophils	60	" "
	Large monos.	180	" "

She was advised to return to bed.

During the next month there were occasional rises of temperature to over 99° F. in the evening, but she commenced getting up on Mar. 18, 1923. The next three weeks were spent in bed or on a sofa, with occasional walks in the garden, but mental depression and tender glands in the neck appeared at times, and for a period of five days (Mar. 29–Apr. 2) she remained entirely in bed with severe depression and weakness.

Apr. 1923. Developed a secondary anaemia and was admitted to hospital on Apr. 24 for a minor operation which was performed on May 14, 1923. While in hospital no further points of importance were discovered beyond the secondary anaemia, which cleared up rapidly after the operation. It was difficult to determine to what extent the fever that was present was due to the original infection, as it also subsided after the operation. X-ray examination at this time showed slight enlargement of the bronchial and mediastinal glands. She left hospital on June 14, 1923, and made steady progress, but with periods of depression and cervical gland tenderness at progressively longer intervals. The temperature charts for Mar., Apr., June, and July showed an irregular periodicity in the fever, and the recurrence of symptoms coincided roughly with the periodic rises of temperature (Chart III).

Sept. 1923. Returned to work.

Dec. 1923. Reported that, though lacking in energy and easily tired, she was well except for mild attacks at about ten-day intervals, when she felt miserable, lost her appetite, and had slight pain and a tight feeling in the

neck. During some of these attacks the cervical lymphatic glands were enlarged and tender.

Case 'S'. Male, aged 40.

Nine days after exposure to infection with *B. tularensis*, had a mild attack of fever and general aching pains, so similar to that seen in Cases 'B' and 'R' that blood was taken for agglutination with *B. tularensis*, and a positive reaction obtained (see Part II). This patient had never been strong and had recently had a severe attack of subacute arthritis. It was therefore not possible to give any details of the phenomena due to the infection, or to gauge to what extent the infection was responsible for any disability that occurred. It was significant, however, that after a year since the probable time of infection this patient suffered from occasional mild attacks of depression, similar to those described in Cases 'B' and 'R', but there was no evidence of enlargement of, or tenderness in, the cervical lymph glands.

Diagnosis.

In making a diagnosis of a rare condition, great care must be taken to eliminate all the less rare conditions before building up the positive diagnosis. The results of the agglutination reactions appear to point definitely to the presence of infection with *B. tularensis* in all three cases, but do not justify the conclusion that the symptoms exhibited were all due to this infection. This is so obvious in Case 'S' that the clinical picture in this instance has not been detailed, while in Case 'R' the onset of a secondary anaemia complicated the picture. Fortunately the period of nine months before this complication arose, and the rapid recovery from it after operation, permit a clear picture of the consequences of the infection to be obtained. In Case 'B' a careful examination of the patient was obtained very early, and a period in hospital allowed of a full investigation. The liability of this patient to recurrent headaches is unfortunate, as it prevents a true estimate of the convalescent period, both as regards the signs of the lingering infection and the extent of time during which some degree of disablement persists.

Case 'R' was the first to acquire the infection, and in consequence of the recognition of the condition as a result of the agglutination tests in Case 'R', the investigations were carried out earlier in Case 'B'. In Case 'B' a definitely positive agglutination was obtained on Oct. 2, over four weeks after the apparent onset on Aug. 31, while on Sept. 22 the agglutination was not sufficiently definite to allow of diagnosis. From the results obtained on the Washington cases a definitely positive agglutination may be expected within three weeks of the onset. Suspicion therefore exists that the onset of tularaemia occurred on Sept. 15, and that the three days of fever and malaise that occurred on Aug. 31 were due to some other infection, such as influenza.

The severe degree of general weakness seen in Cases 'B' and 'R' in the absence of a marked pyrexia, and the complete absence of symptoms or signs localized to any organs or systems, were striking and suggestive of tuberculosis or an enteric infection. In Case 'B', careful investigations at an early stage in the disease failed to obtain any evidence of these infections, while in Case 'R'

the evidence suggestive of such infections was lacking by the time the patient came under observation. The remissions and relapses seen in both cases, and the nature of their work affording exposure to many kinds of infection, necessitated blood cultures, stool and urine cultures, agglutination tests, and animal inoculation. These were carried out in Case 'B', with negative results except in the agglutination reaction with *B. tularensis*.

The absence of localizing symptoms and the pronounced general weakness gave a picture similar to that described by Lake and Francis in the laboratory cases in America, and the initial three days of pyrexia followed by a secondary rise were well seen in Case 'R'. In one respect, however, there is divergence from the picture seen in the American cases, as the subsidence of the fever at the end of about three weeks did not occur in our cases. Another feature common to the two groups has been the long period of convalescence characterized by lack of energy and undue weakness on exertion. In contrast to the general period of three months' disability seen in the American cases, Case 'B' was only able to return to work at the end of six months, while in Case 'R' it was at the end of nine months after the onset that the secondary anaemia occurred and obscured the picture. Cases 2 and 3 in Lake and Francis's series are of interest in that for more than a year they continued to have transient attacks of pain in the back and the calves of the legs respectively, and were only slowly approximating to their usual health, and so were similar to our cases in the prolonged disability, while contrasting with them in the site of the pain noted in the transient attacks, which is definitely located in the neck in both Cases 'B' and 'R'. Case 1 in the American series complained during the acute stages of pain in the throat, and this was also seen in Case 'B' of our series. The absence, in all the laboratory cases, of local lesions, which are the striking features of the naturally occurring infection, the presence of sore throat in those two cases, and the attacks of pain, tenderness, and swelling localized to the cervical glands in Cases 'B' and 'R', are suggestive that the entry of the organism in the cases of laboratory infection may be by the respiratory tract (see Part II).

Full details of the results of the agglutination tests and the method of preparing the bacterial emulsion are given in Part II, and the presence of infection with *B. tularensis* would appear to be established in our three cases.

In Cases 'B' and 'R' the diagnosis of tularaemia is founded on: (1) The presence of an attack of fever not showing the characteristics of any of the recognized infections; (2) but showing characters similar, especially in the slow convalescence, to the cases of laboratory infection in Washington; (3) positive agglutination reactions with *B. tularensis* in the sera; and (4) the history of exposure to infection.

A further point of importance to which attention must be drawn is the fact that all of the workers engaged in the laboratory investigations in America acquired the disease.

PART II. LABORATORY DIAGNOSIS AND PATHOLOGY.

Diagnosis of Tularaemia in Man by Laboratory Methods.

1. *Cases in the field.* In cases of natural infection among farmers and others in infected areas, the symptoms of disease have usually followed the bite of a blood-sucking fly (most probably *Chrysops discalis*) which has previously fed on an infected jack rabbit. Such cases have presented local ulcerative or suppurating areas at the site of the bite, with subsequent swelling and suppuration of the lymph glands draining the region of the bite. In seven such cases investigated by the Washington workers (1 and 2) the diagnosis was readily established both by cultural and serological methods. Material from the local lesion is inoculated into susceptible laboratory animals, guinea-pigs, mice, or rabbits, which later succumb with the characteristic lesions in the spleen and liver. In two of these cases Lake and Francis (10) recovered the organism from the blood, and it was notable that one of these particular cases died, while the other presented a grave condition. In addition, complement-fixation and agglutination tests with cultural antigen always yielded positive results. It is certain, however, that unrecognized cases may occur also in the field which exhibit febrile attacks without obvious local lesions, and, as Lake and Francis suggest, the only practical method of revealing the real nature of these cases is by undertaking systematic serological inquiries.

2. *Cases in rabbit markets or in the domestic kitchen.* A form of infection in which the primary lesion has been an ulcerative condition of the conjunctiva of the left eye has been reported in at least three cases from Cincinnati (12, 17, 18, 19, and 20). The constitutional symptoms were severe, and in addition the glands in the preauricular and cervical regions were swollen. Diagnosis was established by inoculation of susceptible animals with material from the eye lesion. The infected subjects were two females who had dressed rabbits for the family dinner and a meat cutter in a restaurant. Other cases without ocular lesions, but presenting enlarged glands or some history of a sore on the fingers, have been reported, one a worker who dressed rabbits in the Washington market (6), and another a woman who manipulated rabbits in the kitchen for family consumption. The diagnosis in these cases presented no difficulties, both cultural and serological methods being available.

3. *Cases in the laboratory.* Laboratory diagnosis in the six cases reported (10) from the Washington Public Health Laboratories was necessarily confined to serological analysis in the absence of local lesions from which material for experimental inoculation might be obtained. Complement-fixation and agglutination tests with antigen prepared from cultures of *B. tularensis* were employed with convincing results. Blood taken from three of the cases during the febrile stage yielded negative results in guinea-pigs. Some details of the diagnosis in these six cases deserve notice.

Case 1 had his first attack in Aug. 1919 while investigating tularaemia

in a field laboratory. Eighteen months later, when opportunity for serological testing was available, his serum gave a definitely positive reaction. In Jan. 1922 this person, who had continued his work in the laboratory after recovery, had a second attack following the development of a red tender papule in a crack on the right index finger, with subsequent swelling of epitrochlear and axillary glands. Constitutional symptoms were not notable in this second attack. Bloody fluid escaping from the incised papule was inoculated into guinea-pigs with positive results.

Case 2 also contracted infection in the field laboratory in Utah in July 1920. A year later his serum reacted positively. There had been no localizing symptoms.

Case 3 contracted infection in the laboratory at Washington in July 1920, forty-three days after starting work on tularaemia. Serological tests made at intervals during 1921 were all positive.

Case 4 took ill in April 1921, ninety-eight days after starting tularaemia investigations. Serological tests from an early period in the disease were positive.

Case 5 contracted the disease seventeen days after exposure, on April 28, 1921. About the end of May he was sent home from hospital to convalesce. On July 4 he was killed in a railway accident, and we are informed that autopsy revealed no lesions suggesting active or healed tularaemic infection.

Case 6 contracted the disease in July 1921, eighty days after commencing this kind of work. Serological tests were positive.

Antigen employed for agglutination tests in these cases. This was a suspension of a *B. tularensis* culture recovered from a human case in the field. It was heated thirty minutes at 56° C. and preserved by addition of 0.3 per cent. tricresol. The material was sealed in glass ampoules and used for all subsequent tests.

Degree of agglutination. The titre reached by the sera of the Washington cases varied according to the stage of the disease. Thus Case 4 examined on the thirteenth day of illness gave a titre of 1 in 50, but eighteen days later the titre reached 1 in 200. Case 5 examined nineteen days after onset gave a titre of 1 in 400. No control serum gave a trace of agglutination even at 1 in 10.

Permanence of agglutinins. Two cases at periods of twenty and fifteen months after onset still gave positive agglutination at 1 in 50, while another, twelve months after onset, gave a titre of 1 in 25. Case 1, which had given positive results on Jan. 1921 (1 in 100) and June 16, 1921 (1 in 100), yielded a completely negative reaction in June 1922, i.e. two years and ten months from onset, and that too in spite of the fact that he had passed through a second attack in Jan. 1922 without constitutional symptoms (see above).

In all these cases complement-fixation tests gave consistently corroborative evidence, but the general conclusion arrived at was that agglutination tests were perfectly satisfactory and should be given preference.

Laboratory cases at Lister Institute. A culture of *B. tularensis*, an egg-yolk

medium, was received from Washington by the Curator of the National Collection of Type Cultures in May 1922. Guinea-pigs were readily infected and the virus maintained by animal passage, while at the same time attempts were made to secure fresh cultures from the infected animals. These attempts had not definitely succeeded when the first illness occurred among the staff. As exact diagnosis was imperative in an illness so indefinitely characterized clinically, one of us (Ledingham) devised a serviceable antigen for serological tests by the following method. The spleens and livers of infected mice teemed with *B. tularensis*, and it proved a simple matter to recover from them a pure suspension in saline of the causative organism.

The organs were ground up finely in a mortar with formalized citrate solution and the gross particles of spleen tissue allowed to settle. After further fractional centrifugalization of the supernatant fluid a small white deposit was obtained which was finally suspended in formalized saline. This fluid was sealed in phials and used for all agglutination and fixation tests throughout. The principle employed in recovering *B. tularensis* from tissues was essentially similar to that in common use for isolating platelets—the lightest constituents—from the other cellular blood elements.

Results with this antigen and the sera of the three Lister cases at various dates from onset of illness are here appended (Table I). Control sera gave uniformly negative results in dilutions of 1 in 10.

TABLE I.

Case.	Date of Onset.	Serum of Date.	Dilutions.							
			10	20	40	80	160	320	640	1280 2560
'R'	12.7.22	26.7.22	++++	++	+	—	—	—	—	—
"	—	27.8.22	++++	++++	++++	+++	++	Tr.	—	—
"	—	25.9.22	++++	++++	++++	+++	+++	++	++	—
"	—	25.2.23	++++	++++	++++	+++	+++	+++	++	Tr.
"	—	8.5.23	++++	++++	++++	++++	+++	++	Tr.	—
"	—	26.10.23	++++	++++	++++	++++	+++	+++	+	—
'B'	15.9.22	18.9.22	—	—	—	—	—	—	—	—
"	—	22.9.22	+	—	—	—	—	—	—	—
"	—	2.10.22	++++	++++	++++	++++	+++	++	+	—
"	—	9.2.23	++++	++++	++++	+++	++	+	Tr.	—
"	—	26.10.23	++++	++++	++++	++++	+++	+	—	—
'S'	18.9.22	24.9.22	++	Tr.	—	—	—	—	—	—
"	—	30.9.22	++++	++++	+++	++	+	—	—	—
"	—	26.10.23	++++	++++	+++	+++	tr.	—	—	—

It will be seen that towards the end of the second week from onset, in all cases, very definite positive results were obtained. The titres rose rapidly thereafter and remained high during the tedious period of convalescence. Samples of serum taken at periods of thirteen to fifteen months after onset showed little, if any, reduction from the maximum titres attained.

Comparison of antigens. Through the kindness of Dr. McCoy a sample of the cultural antigen employed by the Washington workers for diagnostic tests was received by one of us in May 1923. It was compared in parallel

experiment with the antigen prepared from the tissue organisms in the mouse. The results with both antigens were practically identical. One such comparative experiment may be adduced, the sera employed being those of the three convalescents bled on Oct. 26, 1923 (Table II).

TABLE II.

Case.	Antigen.	20	40	80	160	320	640	1380
'R'	A	++++	++++	++++	+++	++	Tr.	—
	B	++++	++++	++++	+++	+++	+	—
'B'	A	++++	++++	++++	+++	++	—	—
	B	++++	++++	++++	+++	+	—	—
'S'	A	+++	+++	+++	Tr.	—	—	—
	B	+++	+++	+++	+	—	—	—

A = Antigen prepared from mouse spleen.

B = Antigen prepared from culture of *B. tularensis* (McCoy).

It may be added that the blood from the first case was inoculated into guinea-pigs with negative results. The sputum from the third case, 'S', during the acute stage, when a troublesome cough was present, was inoculated into a guinea-pig which died a few days later showing the characteristic mottling of spleen and liver. Owing however to the fact that work on tularaemia had to be closed down completely (Oct. 1922), no attempt was made to deal further with what might have proved an interesting line of investigation from the standpoint of transmission of this disease to workers under laboratory conditions (see below).

Tularaemia in Animals: Mode of Transmission, &c.

This communication deals mainly with tularaemia as it manifests itself in man, but as the disease is primarily one affecting certain animal species in nature, some brief reference is necessary to the accumulated data of the Washington workers, to whose labours both in the field and in the laboratory our knowledge of the disease is largely due.

It was in the course of his search for plague infection in ground squirrels (*Citellus mollis*) in California that McCoy (15) (1911) noted the occurrence of another plague-like disease affecting these animals. The term 'plague-like' was abundantly justified in view of the presence, in animals dying of the naturally acquired infection, of buboes and white or yellowish foci of necrosis in spleen and liver, the former organ being likewise much enlarged. Lung lesions were rare, and the fact is noted by McCoy as an important point of distinction from plague-infected cadavers. The disease in other areas (e.g. Utah) has since been found to affect jack rabbits, and human cases have occurred in the same locality. From Francis's analysis (2) of a series of rabbits found infected in Utah (1920) it would appear that buboes were not found, though in other respects the lesions were similar to those in the ground squirrels.

So far, the disease as a natural infection of certain rodents is confined to the United States, though possibly further investigation may show a wider distribution. Even in the United States its distribution is now known to be considerably wider than at first supposed, and as the result of recent examination of rabbit carcasses reaching the Washington market from various parts of the country (Francis (6), 1923) infected foci would seem to be multiplying. According to Francis foci have now been found in California, Utah, Wyoming, Idaho, Colorado, Southern Indiana, Ohio, Tennessee, North Carolina, and Washington (D.C.). The human case discovered as noted above in the Washington market volunteered the statement that he was suffering from 'rabbit fever' and that the condition was well known among market men.

Animals which have proved to be susceptible to experimental infection include guinea-pigs, rabbits, and mice, which succumb invariably after a few days' illness and exhibit the characteristic lesions in the spleen and liver. Cats, dogs, and pigeons are said to be resistant. Domestic animals such as the calf, swine, and goat are not affected, though the sheep would appear from McCoy's experiments to show some degree of susceptibility.

Transmission. It has been found experimentally that a variety of blood-sucking parasites may convey infection from sick animals to healthy. The rat flea (*Ceratophyllus fasciatus*) and the squirrel flea (*Ceratophyllus acutus*) were found by McCoy and Chapin (16) (1912) to be capable of conveying infection from infected guinea-pigs to healthy animals, and since then the results of an extensive series of investigations on experimental transmission, carried out by Francis and Mayne (9) (1922) and Francis and Lake (8) (1922), have shown that *Chrysops discalis* (a biting fly common in Utah), the rabbit louse (*Haemodipsus ventricosus*), the bed-bug (*Cimex lectularius*), and the mouse louse (*Polyplax serratus*) are all capable of transmitting infection under laboratory conditions. The fact that natural parasites of the rabbit and mouse can transmit disease under such conditions goes far to explain the survival of the disease in rodents in nature.

Morphology and culture of B. tularensis. The organism is a very minute cocco-bacillus, rod-shaped forms being more prominent in early culture and in infected animals examined immediately after death by chloroform. The organism as seen in smears from spleens of dead animals and in histological preparations (see below) has a predominantly coccoid appearance. In spleen smears the organism measures according to McCoy and Chapin $0.3 \mu-0.7 \mu \times 0.2 \mu$. Measurements in culture by Wherry and Lamb (1914) are given as $0.5 \mu-0.6 \mu$ for the coccoid form, and $1 \mu-1.5 \mu \times 0.7 \mu$ for the rod form. Measurements from negatives of films of *B. tularensis* made for one of us by Dr. D. Reid yielded the following figures, the magnification being 3,000: small round forms 0.4μ , barrel-shaped forms $0.33 \mu \times 0.8 \mu$, large round forms 0.66μ (see Plate 24, Figs. 3 and 4). Though small, therefore, they are slightly larger than *rickettsia* bodies found in infected trench-fever and typhus-fever lice, which measure $0.3 \mu-0.5 \mu$.

The organism is Gram-negative and is not readily stained by ordinary

aniline dyes. McCoy employed carbol-fuchsin and aniline-gentian-violet for spleen smears, while Wherry and Lamb obtained good results with aniline-water-Hoffmann's violet or Victoria blue. In our hands Giemsa and Twort's light-green-neutral-red mixture have given excellent results in smears, while the latter stain is the only one which has yielded consistent and beautiful results in defining the organism in tissues (see below).

In 1912 McCoy and Chapin succeeded in obtaining growth on a special medium prepared from egg-yolk sloped and stiffened to an appropriate consistency. On ordinary agar no growth occurs. The egg-yolk medium on which the virus was received from Washington in 1922 did not, in the short time that elapsed before work on tularaemia had to be closed down, yield very definite results. One culture only from a fresh guinea-pig lesion presented the faintest trace of growth, though films from it showed minute rod forms characteristic of early cultural forms. Guinea-pigs only were used at that time, and it is probable that the lack of success in obtaining cultures was due to the fact that in these animals the spleen does not invariably show massive infections as the mouse spleen does. There is further the fact that absence or scarcity of the organism in spleen smears from the guinea-pig is associated with marked infiltration of the organ with polynuclear phagocytes (see below).

The egg-yolk medium has certain disadvantages, arising more particularly from its rather mushy consistency, which interfere with the preparation of antigen for serological purposes. Later Francis (4) (1921) secured a scanty-growth on media such as serum-glucose-agar, glucose-blood-agar, and blood-agar, but when a piece of rabbit spleen was added to these media the growth was equal to that on egg-yolk. More recently the same author (6) (1923) has found that the addition of cystine or cysteine hydrochloride to media such as serum-glucose-agar gives excellent and consistent results both for primary isolation and for successive subculture. On this medium growth occurs in twenty-four hours. The medium serum-glucose-cystine (or cysteine hydrochloride)-agar is thus prepared: fresh beef infusion agar containing 1 per cent. peptone, 1 per cent. agar, and 0.5 per cent. sodium chloride is adjusted to pH 7.3 and kept in stock. Add to stock agar as above 0.1 per cent. of cystine and 1 per cent. glucose, heat in water-bath sufficiently long to melt the agar and sterilize the cystine and glucose. Cool to 50° C. and add 5 per cent. horse-serum. Tube, slant, and incubate twenty-four hours to ensure sterility.

Histology of the experimental lesions in animals. Data on this subject by Woolley (21) (1915) and by one of us (Ledingham (14), 1923) are available. The former author examined the tissues from the experimental animals inoculated by Wherry and Lamb (20) (1914). These animals were mainly rabbits and guinea-pigs, but in Woolley's short paper only a general survey of the histology is given without reference to the species concerned. His results were briefly these: *Skin* (site of inoculation): diffuse necrosis present with invasion by leucocytes. All layers of skin involved. *Lymph glands*: catarrh and cedema of lymph sinuses. Areas of focal necrosis located usually in germ-centres with occasional

adjacent infiltration by polymorphonuclears. *Spleen*: areas of focal necrosis often confluent. Polymorphonuclear infiltration sometimes present round such necroses, but occasionally none. *Liver*: small pale-staining areas diffusely distributed, containing few cells or cells with fragmented nuclei and slight infiltration with polymorphonuclears. *Lungs*: often evidence of lobular pneumonia and diffuse oedema. Earliest lesions were evidently those of coagulative necrosis with some evidence of polynuclear response in the neighbourhood. *Intestinal tract*: no striking lesions. *Kidney*: extreme oedema and cloudy swelling of parenchyma. No necrotic areas seen nor areas of cellular infiltration. Brain, heart, and adrenals showed no lesions apart from congestion. Woolley was unable to demonstrate the organism in the tissues with the stains employed by him. The tissues had been fixed in alcohol or Zenker, and the stains used were Gram, haematoxylin and eosin, eosin and methylene blue, and Borrel.

One of us has studied and briefly reported the lesions in the guinea-pig and mouse. The tissues were removed immediately after death (by chloroform while moribund) and fixed in Dominici's fluid (formalin-sublimate-iodine). The special stains employed were Giemsa, Dominici, and Twort's light-green-neutral-red mixture. The latter stain proved by far the most efficient for definition of the causative organism in the tissue, and striking pictures were obtained, especially in the case of the liver and spleen.

Guinea-pig: *B. tularensis* was easily defined in the lymph spaces of the oedematous area of skin at site of inoculation. Colossal numbers of polymorphonuclears were present, but the organism could not definitely be demonstrated inside the phagocytes. It may be noted that when infection is produced by scarification of the shaved skin, small papules frequently appear as the disease progresses. *Lung*: in some animals multiple haemorrhages were present in addition to areas of consolidation. The pneumonic areas were infiltrated with polymorphonuclears. *B. tularensis*, though here somewhat faintly stained, could be detected among the cast-off endothelia and pus-cells. *Liver*: isolated necrotic foci with infiltrating polymorphonuclears, which were also frequent in the interacinar capillaries. Little change in liver columns. *B. tularensis* not demonstrable (Plate 24, Fig. 6). *Spleen*: the histology of this organ was essentially the same in all guinea-pigs examined, except that, in association with the vast areas of focal coagulative necrosis, polynuclear infiltration was either present or absent. In the former case *B. tularensis* was not demonstrated, while in the latter enormous numbers of organisms were defined either lying free in necrotic areas or in round or oval clumps in the lymph spaces of the reticulum, sometimes also inside swollen endothelial cells (Plate 24, Fig. 5). *Kidney and bone-marrow* showed no special lesions. In one pregnant animal the placenta presented extensive karyorrhectic foci in the neighbourhood of the placental blood sinuses. Sections from a foetus showed no special changes.

Mouse. *Spleen*: massive necroses as in guinea-pig spleen. No polynuclear response was evident and *B. tularensis* was demonstrated in enormous numbers (see Plate 23). *Liver*: this organ showed the most interesting lesion. There were no discrete areas of focal necrosis, but a diffuse invasion of the whole organ

with *B. tularensis*, masses of which lay in the interacinar capillaries and in the liver cells themselves (see Plate 23). *Kidney*: *B. tularensis* was present in large accumulations in the neighbourhood of congested vessels in the hilum. None were seen in the glomerular tufts or kidney tubules. *Lung*: *B. tularensis* was present in perivascular lymph spaces throughout the organ and in the subpleural region. *Lymph glands* showed diffuse areas of necrosis extending inwards from the capsule with clumps of organisms in the vicinity. Brain, testis, and epididymis showed no special lesions. The lesions in experimental tularaemia naturally invite comparison with those met with in plague-infected animals. In the plague-infected rat (see Ledingham (13), 1907) focal necroses of liver and spleen are common features and their histological basis is essentially the same. Liver necroses in the rat plague lesions are, from their number and extent, prominent features of the histological picture, while the splenic necroses are small, scattered, and less discretely marked. In the tularaemia lesions, on the other hand, the splenic necroses were by far the most prominent both in guinea-pig and mouse, and in the latter animal the liver invasion took another form, as described above.

Mechanism of infection of laboratory workers. On this point we do not possess as yet adequate information. All that can be said is that in one case at least (Washington Case No. 1) there was a definite papule in a crack on the finger, but this particular case had had a previous attack. Great care was exercised both in the Washington and Lister laboratories in performing autopsies on animals. In the National Collection the curators removed the dead animals from their cages with tongs and placed them immediately in disinfectants. There was no reason for incriminating some unrecognized infection by the bite of a cimex from an infected cage. While chloroforming animals in the moribund state in order to secure good material for cultural purposes, gloves were always worn. We believe, however, that during this procedure there is some considerable reason for postulating a respiratory infection, as animals not infrequently cough while undergoing anaesthesia. The lungs undoubtedly contain the virus, and it has been shown that the nasal secretions of infected rabbits as well as the urine are infective. It is notable that the third Lister case dated his infection from one exposure only while performing an autopsy on a chloroformed guinea-pig and passaging the virus to another. He remembered distinctly the fact that the animal had coughed in his presence during the anaesthesia. Nine days after, the illness set in. This was his sole association with tularaemia, and indeed he had been out of England for some months until a few days before this incident. It is highly probable in our opinion that a droplet respiratory infection (which of course may be prevented by the wearing of a mask) may explain such cases, as in the very analogous laboratory infections with pneumonic pest.

Summary.

1. The presence of infection with *B. tularensis* has been established in three cases arising in this country from the handling of infected material in a laboratory.

2. In two of the cases the clinical features of the condition have been described.

3. The disease in these cases was marked by the extreme slowness of the convalescence, by recurring mild attacks, and the prolonged period of over a year during which there was at least partial disability for work.

4. An account is given of the serological tests by aid of which the diagnosis of tularaemia in three human cases of laboratory infection was definitely established. The antigen employed in the absence of cultural material was one specially prepared from the highly infected organs of the mouse. Later it was found by comparative test to yield identical results with cultural antigen obtained from Washington. Though tularaemia has not so far been detected in rodents outside the United States, it would be well to remember the possibility of some such origin in obscure cases of human infection with septicæmic features, following 'insect' bites. Serum samples from any such cases should, if possible, be submitted to serological test with tularaemia antigen.

5. A brief account is given of the experiences of the Washington workers in connexion with the artificial culture of *B. tularensis* and its transmission to rodents by various biting insects under laboratory conditions.

6. The histology of the lesions in guinea-pigs and mice is discussed in detail, particular reference being made to (1) the close resemblance of the lesions to those caused by *B. pestis*, (2) the presence or absence of polynuclear infiltration in the neighbourhood of necrotic foci in guinea-pig organs and the corresponding absence or presence of demonstrable virus, and (3) the diffuse infiltration of the mouse liver with *B. tularensis* and the invasion, by the latter, of the actual liver-cells.

7. The probable mechanism of infection in laboratory workers is discussed.

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DESCRIPTION OF PLATES.

PLATE 23, Fig. 1. Liver of infected mouse. Fixation by Dominici. Stain, Twort's light-green-neutral-red mixture.

Note (1) Invasion of liver cells by *B. tularensis*.

(2) Clumps of *B. tularensis* in endothelioid cells and also free in interacinar capillaries.

Fig. 2. Spleen of infected mouse. Fixation and staining as above. Shows the edge of a necrotic focus with clumps of *B. tularensis* in endothelial cells and free.

PLATE 24, Fig. 3. Emulsion of *B. tularensis* extracted from mouse spleen and agglutinated by serum of human case. Stain, Giemsa. $\times 2,000$.

Fig. 4. Ditto. $\times 2,850$.

Fig. 5. Guinea-pig spleen showing necrotic focus with massive karyorrhexia. $\times 500$.

Fig. 6. Guinea-pig liver showing necrotic focus with infiltrating polymorphonuclears. $\times 400$. (Photomicrographs by Dr. D. Reid.)



Fig. 1.

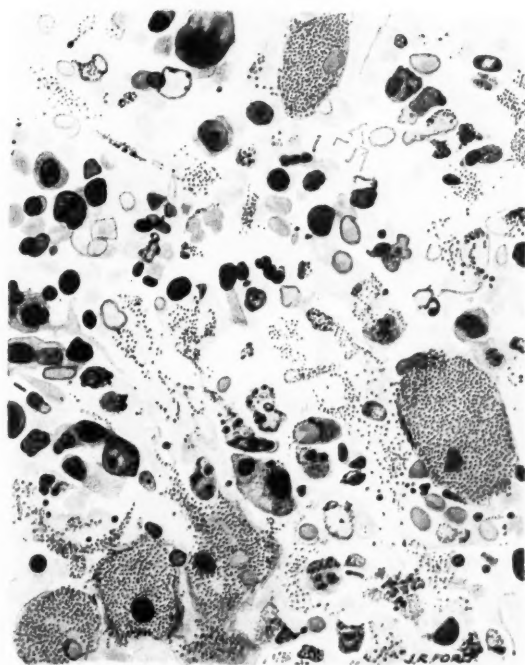


Fig. 2.

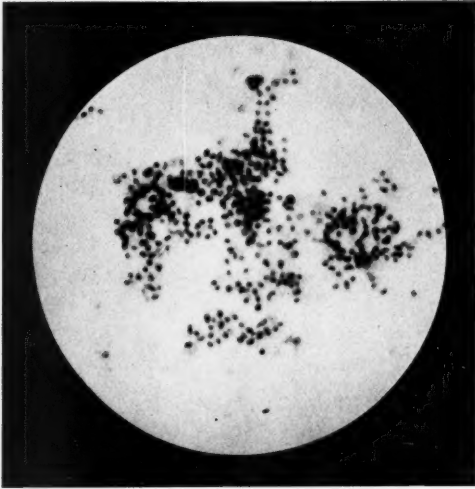


FIG. 3

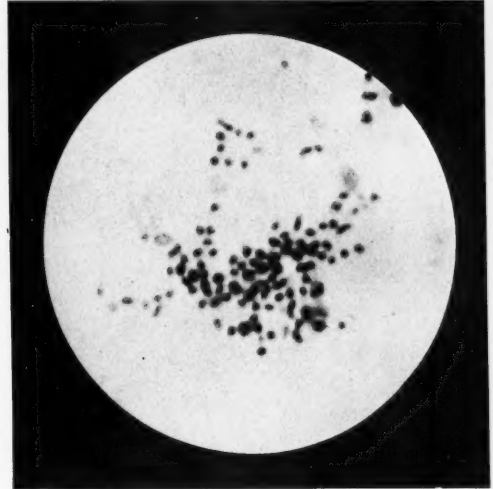


FIG. 4

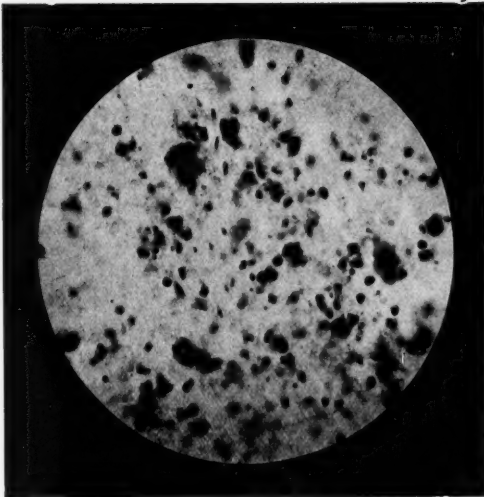


FIG. 5

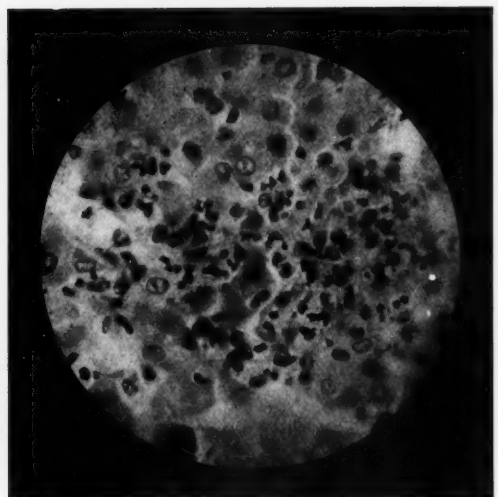


FIG. 6

ON PROGRESSIVE LENTICULAR DEGENERATION (HEPATO-LENTICULAR DEGENERATION)

BY J. G. GREENFIELD, F. J. POYNTON, AND F. M. R. WALSHE

With Plates 25-28

1. *Introductory.*

THE publication in 1912 of Wilson's monograph (22) on the disease which he named progressive lenticular degeneration marked an important advance in our knowledge of the symptomatology and pathology of diseases of the corpus striatum, and by directing the attention of neuro-pathologists to that region of the brain has been the prime factor in the intensive study of the subject, during the past decade.

- Progressive lenticular degeneration is a fatal malady characterized by the progressive development in adolescents or young adults of widespread tremor and rigidity of the skeletal musculature, defects of articulation and deglutition, spasmodic weeping and laughing, a slight degree of dementia, and by the complete absence, in uncomplicated cases, of any true paralysis, or of those alterations in the reflexes which we associate with lesions involving the pyramidal system. Pathologically, the nervous lesion in Wilson's cases consisted of bilaterally symmetrical degeneration of the lenticular and caudate nuclei, with a minimal involvement of the globus pallidus. In addition, the liver constantly showed a profound degree of multilobular cirrhosis which was clinically latent.

In the recognition of a new disease it is inevitable that only those cases can be identified which correspond closely to a single clear-cut clinical and pathological picture. Subsequent investigations usually reveal that both lesion and symptom-complex present appreciable variations from case to case, and the determination of these variations is necessarily a matter of time. This has been no less true of progressive lenticular degeneration than of other maladies of the nervous system, and it is not surprising that the investigations of the past years have raised many fresh problems for solution, and have deprived our notions of the malady of some of their original precision. Another important factor in complicating the questions raised in this way has been the practice of German neurologists of identifying a condition known to them as 'pseudo-sclerosis' with the disease brought to notice and described by Wilson.

The term 'pseudosclerosis' was coined by C. Westphal (21) in 1883 to describe two cases observed by him in which the clinical picture bore certain resemblances to that of disseminated sclerosis, but in which the macroscopic examination of the brain did not reveal the lesions characteristic of this disease. The state of the liver was not mentioned by Westphal. In 1898 and 1899, Strümpell (14, 15) revived the term in connexion with three cases presenting disorders of motor function, with negative pathological findings in the nervous system. In one of these the liver showed syphilitic lesions, in the other two this organ was normal. Of these five cases Wilson aptly remarks that 'they include the most diverse conditions and are quite valueless as far as the derivation from them of any clear-cut clinical and pathological picture is concerned' (23). Up to the year 1911 this stricture applies to all cases so diagnosed, and the term clearly became a lumber-room for various incompletely examined and obscure conditions. The cases so named present no more in common than any heterogeneous collection of motor nervous disorders might do, and in none of them was hepatic cirrhosis observed. In 1903 Fleischer (3) published the clinical description of a case of greenish pigmentation of the cornea in a young man, the subject of symptoms regarded as those of disseminated sclerosis. The pathological report on the case was published in 1909 (4), and such superficial examination of the nervous system as was carried out was negative, but the liver was cirrhotic and the spleen enlarged. In 1912 Fleischer gave a more detailed account of this case under the title 'On a hitherto unknown disease related to pseudosclerosis' (5). The symptom-complex is described as consisting of muscular rigidity and tremor, defects of articulation, and some dementia. The microscopic examination of the cornea is detailed and the pigmentation described.

In the previous year Voelsch (17), under the same title, described the case of a girl of 17, the subject of dysarthria, tremor, and rigidity of the musculature, a mask-like facies, slowness of voluntary movement, dementia, and a complete absence of pyramidal tract signs. The examination of the brain was negative, but the liver was cirrhotic. From this date, which is contemporaneous with the publication of Wilson's paper, the term 'pseudosclerosis', while still retained for the diverse and obscure cases of Westphal, Strümpell, and others, has been employed by German writers to indicate a condition characterized clinically by muscular rigidity, tremor, defects of articulation and deglutition, a mild dementia, and (in some instances only) corneal pigmentation. Pathologically, hepatic cirrhosis is constant in cases so diagnosed. The nervous system has revealed no discoverable lesion in some cases, and in others one essentially the same as that described by Wilson. It is interesting to note in passing that the brain from Fleischer's case, re-examined by Spielmeyer (13) in 1920, presented a lesion regarded by the latter as indistinguishable from that of progressive lenticular degeneration. From this brief *résumé* we see that the modern connotation of the term 'pseudosclerosis' differs essentially from its original one, a fact apparently not fully appreciated by those who use it. The

majority of authors now assume that a single disease is in question, whichever of the two terms be employed, and Hall (7) has coined the term 'hepato-lenticular degeneration' to replace both. Wilson, however, believes that two distinct diseases exist between which there are essential pathological differences, the discussion of which we must defer to a subsequent section.

The principal components of the symptom-complex of hepato-lenticular degeneration have already been enumerated. In all seventy cases have been clinically reported, and of these thirty have been investigated pathologically. In each instance hepatic cirrhosis was found, and we may take this series of verified examples as the basis of a brief clinical analysis of the disease.

It is essentially a malady of youth and early adult life. The *age of onset* ranges from ten years to twenty-five. The most acute case lasted for approximately five weeks from the date of onset, while the most chronic lasted for eleven years. The average *duration* is from one to three years, and the issue is invariably fatal. In his original study Wilson divided his cases into acute and chronic groups, and this classification has been borne out by subsequent experience. There are no essential clinical differences between the two groups. In the series under discussion the *sex incidence* is mainly upon the male side, but if we include all clinically diagnosed examples of the malady the sex incidence is approximately equal. A familial element was present in approximately half of the total of seventy cases, but in the verified series in a much smaller proportion. The involvement in these was of a sister or a brother. A hereditary history was present in two of the unverified cases, but was absent from the rest.

Nothing is certainly known of the nature and pathogenesis of the disease, which is the first in which a constant association of a hepatic with a cerebral lesion has been observed. Wilson believes that it is toxic in origin, the liver being the seat of the primary pathological process. According to this view the cerebral lesion is the result of a selective action upon the corpus striatum of a toxin produced in the liver. There is, however, no conclusive evidence yet available on this point, nor is there any satisfactory alternative hypothesis. In almost every case *tremor* is recorded as the initial symptom, and in all but three it was a prominent symptom throughout the course of the malady. In incidence and character it resembles the tremor of paralysis agitans, and therefore no further reference to it is necessary. In Economo's case (2) no involuntary movements were present at any time. In the case we are about to describe tremor was a late, localized, and relatively transient symptom, while in Thomalla's case (16) powerful and widespread writhing movements of trunk and limbs dominated the clinical picture throughout the illness. This case was diagnosed during life as one of torsion spasm (torsion dystonia, dystonia musculorum deformans), but the Vogts' examination of the brain revealed a lesion identical with that described by Wilson in the brain, as well as hepatic cirrhosis, so that we may regard the case as a clinical variety of progressive lenticular degeneration. Side by side with the development of tremor

is that of *rigidity*. This, also, closely resembles the rigidity of the musculature in paralysis agitans. It is progressive and ultimately renders the patient immobile and helpless. True contracture finally sets in and fixes the subject in the general attitude of flexion into which the rigidity moulds him. Like the rigidity of paralysis agitans, it affects the skeletal muscles diffusely, and is not associated with those alterations in the reflexes which we find after involvement of the pyramidal system. Similarly, it is not associated with any true paralysis, though all voluntary movements are limited in range and rapidity by it, and are readily fatigued. Other manifestations of the rigidity are the *dysarthria* and the *dysphagia* which are such prominent symptoms of the malady. Complete *anarthria* is soon established, and in two cases was even the initial symptom. When this stage is reached, the patient's facies is very striking. The countenance is expressionless and fixed, the mouth half-opened with saliva trickling from the angles. The tongue can be protruded only slowly and incompletely, and from time to time the slow spasms of silent weeping or laughter pass across the face. The *reflexes*, in uncomplicated cases undergo no qualitative change, though when rigidity becomes extreme it may be difficult or even impossible to obtain the tendon-jerks. As a rule the latter are active. Clonus is not present. The abdominal reflexes, also, are retained, unless rigidity of the abdominal wall precludes their presence. The plantar responses remain flexor in type, except in those cases in which the lesion involves the internal capsule. There are no objective sensory changes. A moderate degree of *mental impairment* is characteristic of the malady at some stage of its course, and may be best described as simple reduction or dementia, associated with the emotional overaction seen in the spasmodic laughter and weeping. An inconstant symptom, of which the significance is still obscure, is *corneal pigmentation*. So far this has been reported in but two verified cases diagnosed as progressive lenticular degeneration, and in three of 'pseudosclerosis'. The unfamiliar nature of the phenomenon and the ease with which it may escape detection may be in part responsible for the relative infrequency of its reported occurrence. It consists in a narrow zone of greenish translucent haze at the limbus of the cornea, merging gradually into cornea of normal transparency as it is traced towards the centre. It is approximately 2 mm. in diameter. On oblique illumination of the eye, it was seen to cast a faint but distinct shadow on the subjacent iris in the case to be described, and its occurrence in an unequivocal case of progressive lenticular degeneration has an important bearing on the question of the identity of this disease with 'pseudosclerosis'.

The *multilobular hepatic cirrhosis* which is a constant feature of the post-mortem examination of cases of the disease is clinically latent, and such hepatic function tests as have been performed have not sufficed to render its recognition possible during the life of suspected cases.

In the terminal stages of the malady, the patient becomes extremely emaciated and quite helpless. Incontinence of urine and faeces may be terminal phenomena, but are not characteristic elements in the symptom-complex. In

the chronic cases the course of the malady may be afebrile, but in the acute cases fever and rapid wasting are recorded, and have led Wilson to regard the disease as toxic in origin.

II. *Clinical.*

The patient, a girl of 15 years, was admitted to University College Hospital under the care of one of us (F. J. P.) on November 1, 1920, approximately a year after the onset of her symptoms. In the previous November she had dropped an iron jug on her right foot, causing a short deep cut on the dorsum and mesial side of the great toe. This took six weeks to heal completely, and she received out-patient treatment for this period at the local hospital. Within a few days after healing was complete her mother first noticed that the girl's mouth was constantly open, even during sleep, and that she was dribbling. About two months later her speech became 'thick' and her voice weak, and as these symptoms did not improve she was taken to a doctor early in 1920 'to see what was wrong with her throat'. At this time also there was some question as to a slight weakness of the right arm, but no precise details were available at the time she came under observation as to the degree and nature of this. During 1920 she became worse and it was difficult to understand what she was saying. Occasionally, also, she seemed to have some difficulty in swallowing. Such was her condition when she entered hospital in November 1920.

Her previous health had been good, and according to her mother she was of a 'bright and lively disposition'. She had had measles and chicken-pox in early infancy, and when she was ten years old her tonsils and adenoids were operated upon. During 1918 she was confined to bed for two days with a trivial ailment which was diagnosed as influenza and from which she recovered completely. She had never menstruated. Both parents are alive. The patient is the youngest of three children, the other two, a brother and a sister, being healthy. The parental family history revealed nothing of importance.

On examination the patient lay comfortably in bed and was free from all pain. The secondary sexual characteristics were of normal development for her age, but she was somewhat thin and stunted in growth. Her face wore a vacant, expressionless stare, but when spoken to a wan smile passed slowly across it. The mouth was half opened and saliva trickled from the angles. There was no apparent abnormality of thoracic or abdominal viscera and the urine was normal. The Wassermann reaction was negative.

Mentally she was inclined to be childish. She was perfectly oriented and answered questions (with such power of articulation as she possessed) rationally. She was strangely apathetic and lay motionless and still all day, smiling when she was spoken to. The visual fields and acuity and the fundi were normal. Hearing was of normal acuity. The pupillary reactions and ocular movements were normal. She could close her mouth when urged to do so, but the lips never met over the approximated teeth. She could close her eyes, and the range

of facial movement was not appreciably defective apart from inability to close the lips or to wrinkle the forehead. The tongue was a small organ and moved slowly, and she could not protrude it beyond the line of the teeth. Her articulation was profoundly disordered and her speech was almost unintelligible. Deglutition was normal. Laryngoscopic examination revealed weakness of the abductors of the vocal cords.

Her arms lay adducted and flexed across the trunk. The wrists and digits were also flexed and hung down limply when she sat up or stood erect. The legs lay extended and adducted. Power was good, and there was no paresis. The range and co-ordination of all voluntary movements were normal. No involuntary movements were observed. Passive manipulation of the limbs revealed muscle-tone of normal intensity. The abdominal reflexes were brisk and equal on the two sides and both plantar responses were of flexor type. She could stand and walk naturally. Sensation and sphincter control were normal. The tendon-jerks were present, but sluggish.

On the suspicion that the condition might be hysterical in origin, strong faradism was applied to the neck, but there was no change in articulation at the time, and the strangely indifferent attitude of the patient to the procedure indicated that the suspicion was incorrect. Later, however, there was a distinct improvement in articulation. Early in 1921 she was discharged from hospital with her condition unchanged. No definite diagnosis was made, but bulbar palsy or a post-encephalitic syndrome were suggested as possibilities.

She was readmitted in April 1921, by which time the condition had developed to such a degree that she was recognized as a case of progressive lenticular degeneration. She lay curled up in bed in a general attitude of flexion, except that the head was retracted. Her face still wore the same vacant stare and the mouth was opened (Figs. 1 and 2). From time to time a slow fatuous smile passed very slowly across her face, or she had an attack of slow silent weeping in which tears trickled down her face. This spasmodic weeping and smiling persisted until the last few days of the illness. Although she understood simple requests her mental condition was clearly still more reduced than on her first stay in hospital. She was perfectly oriented and recognized those in attendance upon her. There was complete anarthria, and swallowing was slow and obviously required effort. In fact, she had to be propped up to swallow either liquids or semi-solids. Vision and hearing were normal. The fundi were normal. The pupils were equal, central, and circular and reacted normally to light and to accommodation. Ocular movements were normal in range and association, but lateral deviation was slow and poorly maintained. She could not close her mouth fully when requested. The lower jaw could not be fully depressed by the observer on account of tonic spasm in the masseters. Facial movements were limited in force and range, but there was no gross facial paresis and the eyelids could be approximated. The tongue was as before. The patient was generally emaciated, but there was no localized muscular atrophy. The arms lay flexed as before, but they were now in strong tonic spasm, and full extension

at the elbow required force and was painful. The right wrist was fully extended, the left flexed, and the digits on both sides were clenched in the palm, enclosing the thumb. There was relatively little rigidity in the forearm muscles, so that the wrists and digits could be freely moved passively. Voluntarily the patient could just raise the arms to the vertical, the elbows remaining in half flexion. The grasp was fair, but she could not extend her fingers. There was a constant fine rhythmical tremor of flexion extension of the wrists, the right oscillating round a position of extension, the left round one of flexion. The digits were not involved. The rate was five per second. The legs lay flexed, turned over to one side and approximated. The feet were both fully plantar-flexed, the right hallux fully dorsiflexed, the left plantar-flexed. The limbs could be extended readily, both voluntarily and passively, and there was only the slightest increase of muscle-tone. She could stand and walk without support, but when erect the kyphosis of the dorsal spine persisted, and she was markedly bowed forward. No sensory changes were detected. The arm-jerks were present but sluggish, the knee- and ankle-jerks of normal facility, the abdominal muscles were so rigid that no reflex response could be obtained from them, and the plantar responses were both perfectly normal in form. Sphincter control was perfect.

From this time the patient went rapidly downhill. By the 16th of July she was no longer able to stand unsupported and was quite unable to walk. Her trunk was flexed so that she would have fallen forwards unless held up. The head remained rigidly retracted until the end. The lower limbs were now becoming very feeble and rigid. As she lay in bed they were in constant full flexion-extension movement, so that the knees rubbed together and one or other knee was pressed up against her chin. At times both lay in this position and oscillated slowly and in movements of wide amplitude. The feet remained as before. In the upper limbs the tremor had ceased entirely, but the limbs remained otherwise as before. The fingers could still be fully extended. Her general attitude of flexion as she lay in bed was extreme, and the back could not be straightened out. Definite contracture began to develop in the limbs.

After the condition was recognized an examination of the eyes was made. The iris was clear in texture and greenish in colour. At the limbus of the cornea there was a zone, of approximately 2 mm. width, in which the cornea was hazy, translucent, and of a greenish-brown lustre. When the eye was illuminated obliquely the faint shadow of this zone was clearly thrown on to the subjacent iris. The inner border of the pigmented corneal zone was not sharp, but passed insensibly into cornea of normal transparency. The condition was similar and of equal intensity in both eyes, and its presence was confirmed by several observers on many occasions during the last month of life.

On August 1, although her general condition was rapidly failing and she was becoming profoundly emaciated, the physical signs were not greatly changed. The general flexion contracture was now pronounced, although the flexion-extension movements of the legs continued. She still understood what was said to her, but was almost constantly either weeping or smiling, and was completely

aphonic and anarthric. The tendon-jerks were all absent, and the plantar responses remained normal in type. She remained conscious until a few hours before death. The liver dullness was not definitely abnormal to palpation and the spleen was not palpable. There was no jaundice, ascites, or venous obstruction. On August 3 congestion and oedema of the lungs developed, the temperature began to rise for the first time and kept at about 103° F. until death, which occurred on August 7. Up to within a few hours of this she was fully conscious and understood what was said to her.

Post Mortem.

The examination was performed twelve hours after death. The body was emaciated and in rigor mortis. The heart was small, weighing 140 gm., but was otherwise normal. The aorta was small but healthy. The lungs were normal, except for congestion at the bases. The thymus tissue was atrophied. The thyroid was normal. The alimentary canal presented no abnormality. The kidneys and suprarenal glands were normal. The *spleen* weighed 140 gm. and was normal in appearance on the surface and on section. The uterus was very small, being only 4 cm. in vertical length. The ovaries were small but otherwise normal. The *liver* was small, weighing 935 gm. The capsule was slightly wrinkled, and the surface was studded by small nodules projecting slightly above the surface, packed closely together and of 0.5 cm. in diameter. The inferior surface and that of the Spigelian lobe were most affected. On section it showed the characteristic appearance of multilobular cirrhosis (Fig. 3). The organ was extremely tough in consistence.

On *microscopic examination* the *spleen* showed chronic congestion with some thickening of the fibrous tissue septa. The *liver* showed a fine multilobular cirrhosis of a rich cellular type. The strands of thickening which separated the lobules consisted of fibroblastic cells with numerous blood-vessels and a few new bile capillaries. Fully-formed fibroglia fibres lay among the fibroblastic cells, but were comparatively scanty. The thickness of the septa varied in different parts of the organ, being half the diameter of a lobule in some regions. In others there was only slight cellular proliferation in the portal spaces and the interlobular septa were of normal thickness. The liver cells were practically normal. Some contained granules of brown pigment, especially round the hepatic veins, and some fatty infiltration of scattered groups of cells, both at the centre and at the periphery of the affected lobules, was also seen (Fig. 4).

The *heart-muscle* showed no abnormality. In most of the fibres a few granules of brown pigment were to be seen at either end of the nucleus.

The pituitary. The anterior part contained no colloid in the vesicles, but the pars intermedia contained a large mass. The pars nervosa was normal.

The cornea. The pigment in Descemet's membrane which was responsible for the greenish tinge of the periphery of the cornea during life was clearly seen microscopically as very fine dark-brown granules (Fig. 5). These were restricted

to the membrane, being absent both from the cells of the corneal substance and from the surface epithelium on the inner surface. They were most numerous at the periphery of the cornea and were entirely absent from the central half. The micro-chemical reactions of the granules were studied in paraffin sections by the methods adopted by Fleischer (4) and similar results were obtained. (i) The granules were not decolorized by four days' treatment with hydrogen peroxide (ten vol. strength), which completely decolorizes melanin pigment. (ii) They did not give the Prussian blue reaction for iron. (iii) They were decolorized by two hours' treatment in 25 per cent. HCl, which leaves melanin intact. One hour's treatment with 12 per cent. HCl failed to affect them.

Nervous system. The meninges and the surface of the brain presented no abnormality whatever. The brain and cord were fixed in 10 per cent. formalin saline solution and were cut across after fixation. A horizontal slice was first made through both hemispheres under the corpus callosum and through the basal ganglia (Marie's *coupe d'élection*) (Fig. 6). The left hemisphere was then cut in coronal sections (Fig. 8) and the right in horizontal sections, the pieces in either cases being about 5 mm. in thickness.

At first sight no obvious abnormality was apparent, but on closer examination it was seen that the caudate nucleus and the putamen of the lenticular nucleus were shrunken and appeared browner than normal. This change was most evident in the putamen, which had shrunk to about half its normal width. This shrinkage of the largest part of the corpus striatum had reduced the whole area covered by this structure, and as a result of this the lateral ventricle was somewhat dilated, and the curve presented by the external capsule in horizontal section was less convex than normal, and indeed presented the shape of a 'Cupid's bow', being slightly concave at its anterior and posterior extremities (see Fig. 6). In coronal sections across the posterior half of the putamen the outer surface of this nucleus, and in consequence the external capsule, appeared actually concave outwards (see Fig. 8). The bulge of the normal caudate nucleus into the wall of the lateral ventricle was almost completely absent. It was only seen in the region of the head of the nucleus, and was there much less pronounced than normal (Fig. 8).

A comparison of the transverse diameter of these nuclei with those of the normal brain (Figs. 6, 7) showed that the shrinkage of the caudate nucleus was less real than apparent, and that it had been drawn into the brain substance by the greater shrinkage of the putamen. These measurements were made on Marchi sections taken from the right half of the brain, and were compared with similar sections of the basal ganglia of subjects who had died of a variety of conditions. The only available Marchi sections with which they could be compared were those from a case of paralysis agitans that came to post-mortem examination at the age of 61. A comparison of the Marchi sections of this case with those which had been embedded in celloidin without previous mordanting showed that although the Marchi sections were slightly less shrunken than the others, the difference was negligible. It is, therefore, permissible to compare

the Marchi sections of our case of progressive lenticular degeneration with ordinary celloidin sections taken from the brain of a boy of the same age as our patient, who died from a cervical myelitis following many months after an acute ascending paralysis of the Landry type. This patient had been bed-ridden for about six months, and although not so much wasted as our patient (K. W.) appeared to us to furnish a control as nearly as possible comparable in age and in duration of paralysis.

The following measurements of the maximum transverse width of the three chief elements of the corpus striatum were recorded :

Disease.	Caudate Nucleus.	Globus Pallidus.	Putamen.
Progressive lenticular degeneration (K. W., aged 17)	6 mm.	7.5 mm.	4 mm. at centre 5 mm. at anterior end
Myelitis following Landry's paralysis (S. O., aged 18)	7 mm.	7.5 mm.	9 mm.
Encephalitis lethargica (5 days) (G., aged 22)	8 mm.	7.5 mm.	10 mm.
Huntington's chorea (Aged 45 ?)	7.5 mm.	7 mm.	10 mm.
Paralysis agitans (A. C., aged 48 ?)	8 mm.	7 mm.	10 mm.

Our case (K. W.) shows, therefore, a slight but definite shrinkage in the head of the caudate nucleus, and a much greater shrinkage, to about half its normal diameter, of the putamen, the globus pallidus remaining little, if at all, affected. The body of the caudate nucleus was much more shrunken than the head, which was the only part from which comparative measurements could be taken satisfactorily.

Pieces cut in coronal section from the left cerebral hemisphere and longitudinal sagittal sections of the brain-stem were embedded in celloidin without previous mordanting.

The right hemisphere, cut in horizontal slabs, was stained by the Marchi-Busch method, as was also the right half of the brain-stem, which was cut in sagittal sections. We have greatly regretted that the brain-stem was treated in sagittal sections, as the localization of tracts and nuclei was thus made much more difficult. At the same time the pictures given of the whole length of such tracts as the posterior longitudinal bundle and such nuclei as the oculo-motor almost repay the increased trouble of localization.

Left hemisphere. Alum-haematoxylin with van Gieson's counterstain and Nissl's stain were employed on serial sections through the basal ganglia of the left hemisphere. These sections were compared with similar sections from the case of Landry's paralysis already mentioned. A few sections from each slab were also stained by the Loyez method for myelinated fibres, and by Mallory's phosphotungstic acid-haematoxylin for neuroglia fibres.

It may be said at once that the only parts of the basal ganglia which

showed any great abnormality were the caudate nucleus and putamen. The changes in these nuclei were similar in kind, but were more pronounced, and appeared to be of longer duration, in the putamen than in the caudate nucleus. They consisted of degeneration of both the larger and smaller types of nerve-cells with proliferation and enlargement of the neuroglial nuclei. The latter approximated so closely in size and appearance to the nuclei of the smaller nerve-cells that it was often quite impossible to distinguish them from one another, and, in consequence, it looked at first sight as though the small nerve-cells were increased in number. It was certainly impossible to say that there had been any disappearance of these cells, but when one takes into account the great reduction in size of the basal nuclei in question, it appears probable that a certain number of the smaller nerve-cells had disappeared. The large nerve-cells also appeared to be almost as numerous as in the controls, but, allowing for the shrinkage in the transverse diameter of the putamen and the caudate nucleus, we may conclude that about seven-eighths of the large nerve-cells in the putamen, and at least half of those in the caudate nucleus, had entirely disappeared. Of those that remained scarcely one presented an appearance which approximated to the normal. The nuclei were almost always eccentric, usually lying against the cell membrane, and the nuclear membrane was shrunken and crenated. Reniform nuclei were commonly seen, and the nuclein, instead of being collected around the nucleolus as in normal nerve-cells, was scattered in several small knots through the nucleus. The cell body was, either swollen and rounded, or shrunken and obviously disappearing. In most of the cells it was filled with lipochrome granules, but in the more shrunken cells these were not obvious. The Nissl granules of most of the cells had entirely disappeared. In a few cells, especially in the caudate nucleus, a few peripheral Nissl granules could be seen. Satellitosis was a very common feature, and in some places a cluster of satellite cells around an amorphous globoid body or the pale and shrunken remains of a nuclear membrane were the only remaining evidence of the position of a nerve-cell.

The small nerve-cells presented similar changes, but, as has already been said, owing to the loss of Nissl granules and the dispersion of the knots of nuclein throughout the nucleus, it was very difficult to distinguish them from enlarged neuroglial cells. The proliferation and enlargement of neuroglial nuclei were everywhere obvious, but whether owing to prolonged formalin fixation, or to defective early fixation of the deeper parts of the basal ganglia, it was impossible to obtain satisfactory staining of neuroglia fibres in these regions by any method. But the deep tint taken by the caudate nucleus and putamen with Mallory's haematoxylin, and with van Gieson's counterstain, suggested a neuroglial overgrowth in these nuclei. The parts of the caudate nucleus nearest to the wall of the third ventricle stained well with Mallory's haematoxylin and showed considerable proliferation of neuroglial fibres.

The blood-vessels in the putamen and caudate nucleus presented comparatively little abnormality. There was certainly no thickening or hyaline change

in the coats of the vessels. On the other hand, many of the vessels showed collections of degeneration products, either free in the Virchow-Robin space, or in the cytoplasm of some of the cells lining this space. As we did not make any frozen sections of the basal ganglia only those degeneration products which did not dissolve either in absolute alcohol, ether, or xylol remained in the sections, but from their highly refractile nature, as well as from the evidence afforded by Marchi sections of the same region, we concluded that they were, at any rate in part, of a lipid nature.

Similar collections of degeneration products were numerous in the walls of the vessels in the external capsule and the deeper layers of the cortex of the island of Reil. A few vessels, both in this neighbourhood and in the caudate nucleus, showed collections of small round cells within their adventitial lymph spaces, but neither here nor elsewhere in the brain was this a striking feature; it affected a vessel here and there in an apparently arbitrary fashion, and was not definitely related to the other processes of degeneration. The cells forming these perivascular collections were small cells of the lymphocyte or small glial cell type, most probably the latter; no plasma cells were seen among them, and we do not consider them to be in any way indicative of an inflammatory process.

Globus pallidus. In contrast with the putamen the globus pallidus was relatively little affected. We have seen that it was slightly, if at all, atrophied, and its microscopic structure also approximated to the normal. The large cells which characterize it were perhaps rather less numerous than normal, and, except for an excess of lipochrome granules, they presented no abnormality. The neuroglial nuclei were only slightly increased in number, and there was no evidence of overgrowth of neuroglial fibres.

The cerebral cortex showed no alteration either in the appearance or arrangement of the nerve-cells. The blood-vessels were, for the most part, perfectly healthy, but a few of them showed collections of degeneration products within their walls. No foci of 'vascular new-formation', such as were described by Hadfield, were found.

The nucleus ruber also was only slightly affected, but here a comparison with the control brain showed a relative excess of small neuroglial nuclei.

The corpus luyssii showed similar slight evidence of cell degeneration, and was rather thinner than in the control.

In the substantia nigra most of the cells contained normal Nissl granules and an abundance of small greenish-black melanin granules, but in some places melanin granules could also be seen lying in the endothelial cells of the vessel walls.

The cells of the dentate nucleus showed no alteration except an excess of lipochrome pigment and poverty of Nissl granules.

The nuclei of brain-stem and the cortex of the cerebellum showed no obvious abnormality, but here and there throughout the pons and medulla could be seen vessels which showed a considerable degree of perivascular infiltration with small round cells.

Marchi sections. Owing to the relatively short period during which our patient presented severe motor symptoms, we considered that we should obtain most evidence of disease by using the Marchi method rather than the Weigert-Pal. But although the degeneration of myelin sheaths was obvious enough and its distribution to some extent unexpected, the degree to which it had advanced was very slight. In all of the affected tracts it took the form of very fine granules, and had it not been for the presence of these among unaffected tracts and the collection of black staining lipid granules within the vessel walls, we should have been inclined to consider them as artifacts. We have, in fact, discounted them wherever they might have been produced by handling the brain on its removal from the body, and where they were not corroborated by the presence of fatty granules within the vessel walls.

In slabs 2 and 3 of the basal ganglia only a few degenerated fibres were observed. A leash of such fibres was seen at the posterior end of the line of junction of the putamen with the globus pallidus. No degenerated fibres could be seen in the substance either of the putamen or the globus pallidus, but the nerve-cells in these nuclei showed dark staining granules. Similar granules were seen in the walls of the vessels which ran between the putamen and the cortex of the island of Reil. The taenia semicircularis, where it was seen on the ventricular surface between the caudate nucleus and optic thalamus, also showed evidence of degeneration.

In slab 4 degenerated fibres could be seen wheeling round the mesial end of the internal capsule (basis pedunculi) and also passing through the middle of it to the corpus luyssii. The former fibres represented the part of the ansa lenticularis which goes to the nucleus ruber, and the latter in all probability the strio-luysian fibres. There was a slighter degree of degeneration in the fibres of the mesial fillet, and in those of the oculomotor nerves. As regards the latter the degeneration in them was probably due to traction on the nerve as the brain was removed from the body, and may be classed as an artifact. No degeneration of the fibres of the pyramidal tract, of the anterior pillar of the fornix, or of the bundle of Vieq d'Azyr could be seen. The red nucleus and the fibres forming its capsule showed no evidence of degeneration.

At a lower level in the brain-stem the most striking degeneration was seen in the posterior longitudinal bundle. This was seen through all its extent, and was associated with a considerable collection of pigment granules in the vessel walls. There was also a slighter degree of degeneration in the brachium conjunctivum (superior cerebellar peduncle), in some parts of the white matter underlying the cerebellar cortex, and in the corpus restiforme. In the latter two situations the degeneration was probably an artifact, but there is evidence from other cases to suggest that the degeneration in the brachium conjunctivum represented a definite part of the pathological picture.

Summary.

Following a trivial injury to one foot a previously healthy girl of 14 developed an inability to keep her mouth closed, dribbling of saliva, and progressive dysarthria. A year from onset she was observed to have an immobile mask-like countenance, spasmodic weeping and laughter, a half-opened mouth from which saliva trickled, limitation of range and rapidity of movement of facial muscles and tongue, and a maintained flexion attitude of the arms and hands. There was no paralysis, nor any rigidity of the limb or trunk muscles. The reflexes and sensation were normal. During the last eight months of life these symptoms progressed, and she became completely anarthric, developed dysphagia, increased frequency and intensity of spasmodic weeping and laughing, rigidity of the facial and upper limb muscles, a general flexion attitude of the trunk and limbs, tremor of the hands, and finally rigidity and ample slow flexion-extension movements of the lower limbs. Death occurred in the twentieth month of the illness. The malady ran an afebrile course, and there were no symptoms referable to any hepatic lesion. The periphery of the cornea showed a zone of greenish haziness.

Pathologically, the liver showed a profound atrophic multilobular cirrhosis. Naked-eye examination of the brain revealed marked shrinkage of the corpus striatum, involving the putamen and caudate nucleus, the globus pallidus remaining normal in bulk. The affected areas looked granular in texture. Microscopic examination of the brain revealed degeneration of the nerve-cells in the putamen and caudate nucleus, with neuroglial overgrowth. Similar but much slighter changes were present in the globus pallidus and nucleus ruber. Marchi staining revealed degeneration in the tracts leading from the putamen to the nucleus ruber and corpus luyssii, and also of the posterior longitudinal bundle and superior cerebellar peduncle. The corneal pigmentation was due to the presence of fine brown granules in Descemet's membrane at the periphery of the cornea.

Comparison of Pathological Changes in this and other Cases of Hepatolenticular Degeneration.

A survey of the literature shows that the pathological picture of hepatolenticular degeneration, although constant in essentials, is very diverse in details. The only feature which has been constantly reported in all cases is a multilobular cirrhosis of the liver which, in practically every case, has given rise neither to jaundice nor ascites, but is often associated with enlargement of the spleen. A cirrhosis of this kind has been observed in thirty cases, including our own, which have shown symptoms similar to those described by Wilson. We include among these Thomalla's case of 'torsion spasm', because, although differing to some extent in symptomatology, it resembled Wilson's cases so closely in

its pathological aspect that, as we have already said, we cannot put it in a class by itself. But we must guard against the assumption that every case which presents symptoms referable to the basal ganglia and in which asymptomatic cirrhosis of the liver is found is a case of Wilson's disease; for it is known that chronic manganese poisoning causes some of the symptoms of paralysis agitans (mask-like face, propulsion, retropulsion, and rigidity), and that both in man and animals it is associated with asymptomatic biliary cirrhosis. The connexion between this condition and 'progressive' or 'hepato-lenticular' degeneration raises points of great interest in regard to the pathogenesis of the cerebral condition, but these are beyond the scope of this paper.

Of the thirty cases which have come to autopsy, and in which cirrhosis of the liver has been found, sixteen have shown, to the naked eye, bilateral softening and cavitation of the lenticular nucleus. In the other fourteen either the lenticular nucleus has been described as shrunken and browner than normal (as in our case), or no abnormality has been observed on section of the brain. But in every one of those cases in which a careful microscopic examination has been made of the basal ganglia, profound changes have been observed in the putamen of both sides. These have consisted in degeneration and atrophy of the nerve-cells of the putamen, with overgrowth of the neuroglia, but without any evidence of inflammation. In some cases the walls of the blood-vessels have been found to be thickened or hyaline, but in the majority they have been normal, except for the accumulation within the perivascular spaces of the products of degeneration of the nervous tissue. It is, therefore, certain that atrophy and degeneration of the putamen, although not obvious on naked-eye examination of the brain in about half of the cases, is nevertheless a constant feature of the disease.

This association of atrophic degeneration of the putamen and multilobular cirrhosis of the liver in every case has induced Hall, of Copenhagen, to rename the disease 'hepato-lenticular degeneration'.

The other pathological changes are less constant. In very many, probably the majority of cases, the caudate nucleus undergoes a degeneration similar in type to that in the putamen, although of less severity. The globus pallidus is less often affected, but when cavitation is present in the region of the putamen the globus pallidus rarely escapes unscathed, and sometimes even the internal capsule is partially involved; further, since the process of softening and rarefaction affects principally the outer part of the putamen, it is not unusual for the external capsule to be to some extent involved in the process. Changes in the cortex have been less commonly found, but have been present in nine cases. In most of these they consisted in neuroglial overgrowth and the presence of abnormal types of neuroglial cell only, but in that of Hadfield curious small areas of vascular new-formation were described.

Still more rare are changes in the brain-stem and cerebellum. Howard and Royce (9) and Pfeiffer (10) have described changes in the red nucleus, and Westphal (20), Hösslin and Alzheimer (8), Bostroem (1), and Pollak (11) have found degeneration of the dentate nucleus. Pollak's case is worthy of mention

in more detail, as it showed not only very extensive softening of the lenticular nucleus, which spread to both the internal and external capsules, but also a similar condition in the white matter of the cerebellum, which involved some regions of the cortex cerebelli and the greater part of the dentate nucleus: neither vascular degeneration nor evidence of inflammation was present, and the microscopic changes in the lenticular and the dentate nuclei were essentially similar.

In the cornea, the characteristic pigmentation of the membrane of Descemet has been present in five of the cases other than our own which have undergone a post-mortem examination. (It is curious to note that in only one of these, that of Pollock (12), was there any gross change in the lenticular nucleus.) It was present in the two cases which were published by Fleischer before the appearance of Wilson's monograph, in which he did not pay special attention to the microscopic study of the lenticular nucleus; in that of Dziembowski, who found no gross macroscopic or microscopic changes in the brain; and in those of Hall and Westphal, in which degeneration of nerve-cells and neuroglial overgrowth were present in the lenticular nucleus. For some years after the appearance of Fleischer's paper corneal pigmentation was supposed to differentiate the so-called 'pseudosclerosis' from Wilson's 'progressive lenticular degeneration', but the cases of Pollock and of Hall proved that supposition to be erroneous, as both clinically and pathologically they were cases of Wilson's disease.

Our own case is interesting as serving in some measure to co-ordinate the various pathological changes found in other cases. The appearance of the patient was so similar to that of one pictured in Wilson's monograph as by itself to indicate the diagnosis; the age at onset and duration of the disease were each about the mean of Wilson's cases. So far it was a typical case of Wilson's disease. On the other hand, the changes in the brain, though so slight as not to be obvious on naked-eye examination, proved to be almost as extensive as in any case described as 'pseudosclerosis'.

On the other hand, they were most severe in the putamen and caudate nucleus—that is, the only parts of the brain found by Wilson to show gross changes.

The degeneration in the posterior longitudinal bundle and brachium conjunctivum in our case may be associated with the bilateral cerebellar softening described by Pollak, and the changes in the dentate nucleus described by others. Such changes in regions as far apart as the cerebellum and the cortex cerebri show that although the chief brunt of the disease falls on the putamen the pathological process in the brain is not limited to one region or even to one physiological system.

Conclusions.

From the brief historical *résumé* we have given, and from a consideration of the personally observed case which we have described, it seems justifiable to conclude that the malady to which the name 'pseudosclerosis' is now applied

by German writers is no other than the progressive lenticular degeneration described by Wilson. The history of the term 'pseudosclerosis' indicates that the diverse conditions to which Westphal and Strümpell first gave the name cannot be identified with the malady for which it is now employed. For this reason, and even more on account of the essentially vague and misleading nature of the term, it no longer has any proper place in a precise neurological nomenclature, and its retention by German writers has nothing whatever to commend it. The disease in question was first adequately investigated and described by Wilson, and all precise work on the subject dates from the publication of his paper in 1912. Therefore, the name progressive lenticular degeneration given by him to the disease, or Hall's alternative 'hepato-lenticular degeneration', may with advantage be employed.

The investigations of the past ten years, based upon the clinico-pathological study of thirty cases, indicates that the nervous lesion is not always so gross that it is readily discoverable to the naked eye on section of the brain, while histological examination has revealed that it is not invariably confined to the corpus striatum or to its fibre systems. In short, progressive lenticular degeneration can no longer be accurately spoken of as a system disease of the corpus striatum. Nevertheless, within the corpus striatum, the brunt of the disease process falls upon the putamen and to a less extent upon the caudate nucleus. The cardinal elements of the symptom-complex in Wilson's original cases, and in the great majority of subsequently recorded cases, are muscular rigidity and tremor, and Wilson believes that these constitute a pure syndrome of the corpus striatum. However, in Economo's case tremor was absent throughout the course of the malady, in the case we have described it was a late and a relatively transient symptom, while in Thomalla's case of 'torsion spasm' the symptom which dominated the clinical picture was widespread and powerful involuntary movement of the mobile spasm variety. In other words, a lesion almost entirely confined to that part of the corpus striatum spoken of, on phylogenetic grounds, as the neostriatum (putamen and caudate nucleus) may give rise to three main types of motor disorder—rigidity alone, rigidity with tremor, or torsion spasm. C. and O. Vogt have, on the basis of an extensive histological investigation of diseases of the corpus striatum, attempted to elaborate two syndromes of the corpus striatum: a syndrome of the striatum (neostriatum) consisting of involuntary movement, athetosis, choreiform movements, or tremor, and a syndrome of the pallidum (globus pallidus) of which rigidity is the motor manifestation. Further, they have attempted an analysis of these syndromes in terms of the normal functions of the two components of the corpus striatum. From what we have said of the variations of the clinical picture in progressive lenticular degeneration, it is clear that the time has not yet arrived for so precise a localization of symptoms within the corpus striatum, and that a final determination of the functions of this structure is a consummation even more remote.

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DESCRIPTION OF PLATES.

PLATE 25, FIGS. 1 and 2. Clinical aspect of the patient three months before death.

PLATE 26, FIG. 3. The liver. A wedge-shaped piece has been removed from the posterior surface of the right lobe, to show the cirrhotic appearance on section. The weight of the organ was 935 gm.

PLATE 27, FIG. 4. Microscopic appearance of the liver. For description, see text.

FIG. 5. Microscopic section of the cornea, showing thickly-scattered fine granules in Descemet's membrane.

PLATE 28, FIG. 6. A horizontal section of the left hemisphere at the plane of Marie's *coupe d'élection*. The putamen and caudate nucleus, especially the former, are much shrunk and are darker in colour than normal.

FIG. 7. Horizontal section of left hemisphere from a normal brain, showing the normal volume and contours of the components of the corpus striatum.

FIG. 8. Vertical coronal sections of the left hemisphere (anterior surfaces), showing the shrinking of the putamen and its abnormal concave lateral border. The caudate nucleus is also much shrunk. The globus pallidus is of normal volume.

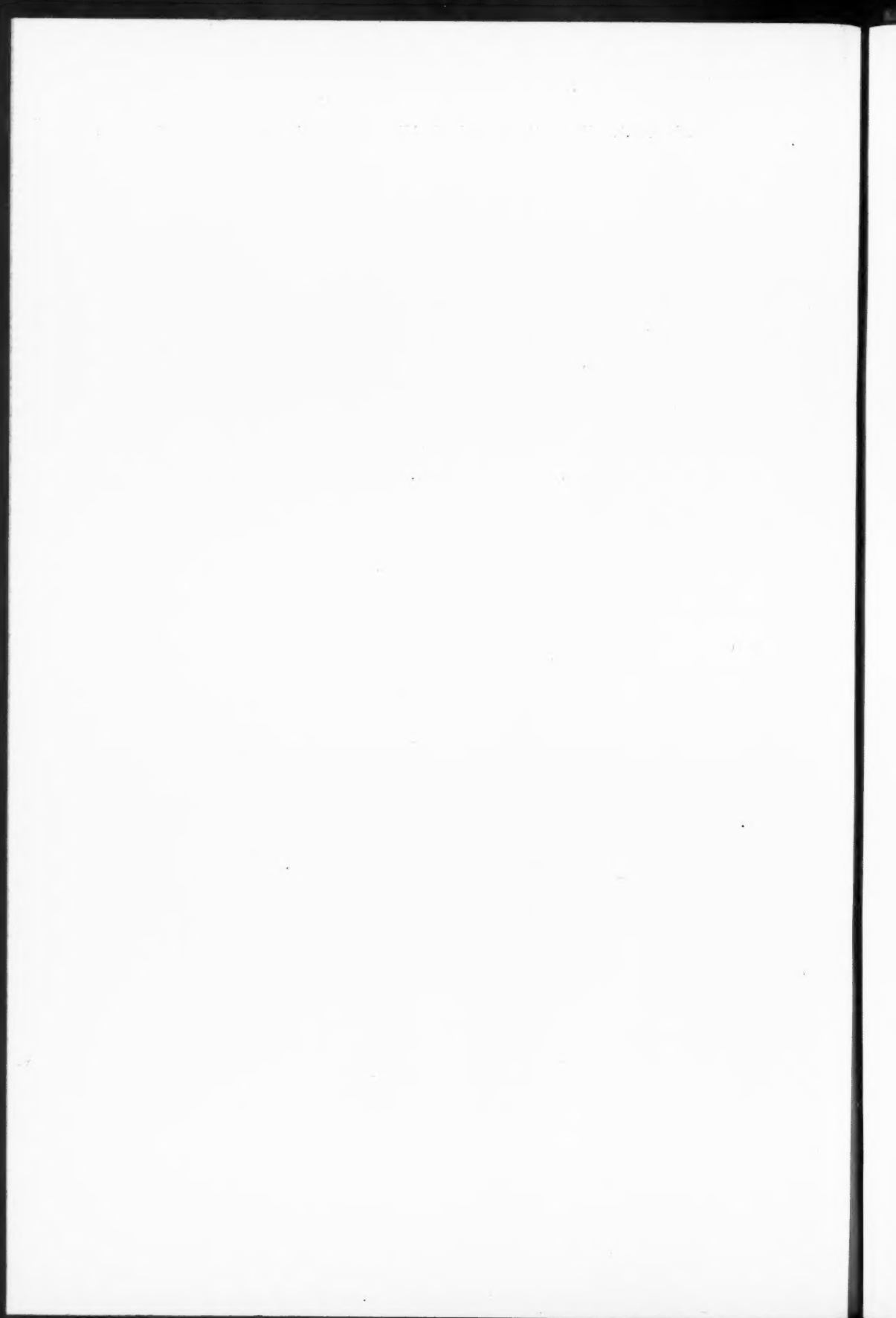




FIG. 1



FIG. 2

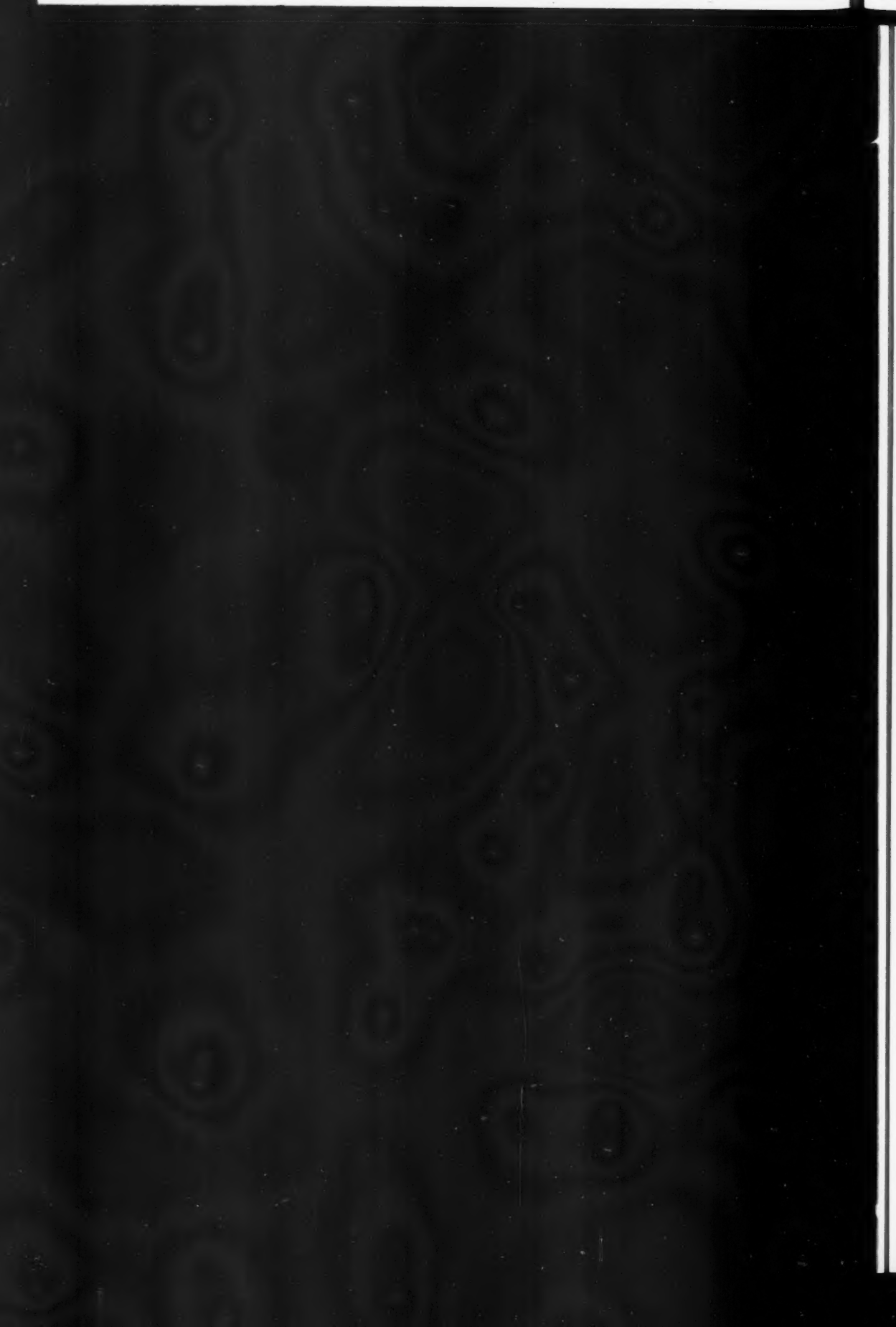




FIG. 3

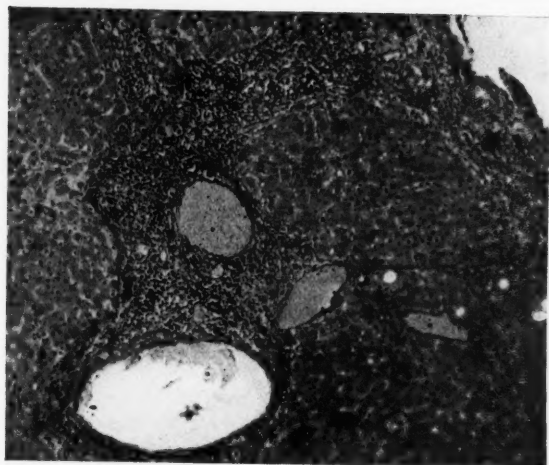


FIG. 4

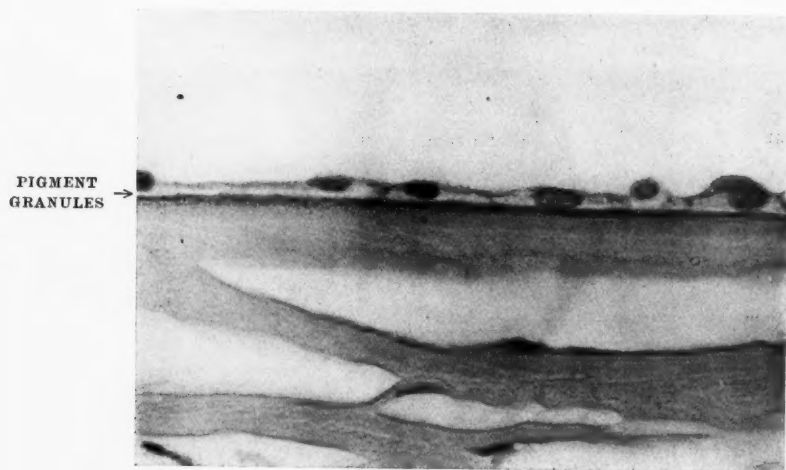


FIG. 5



FIG. 6



FIG. 7

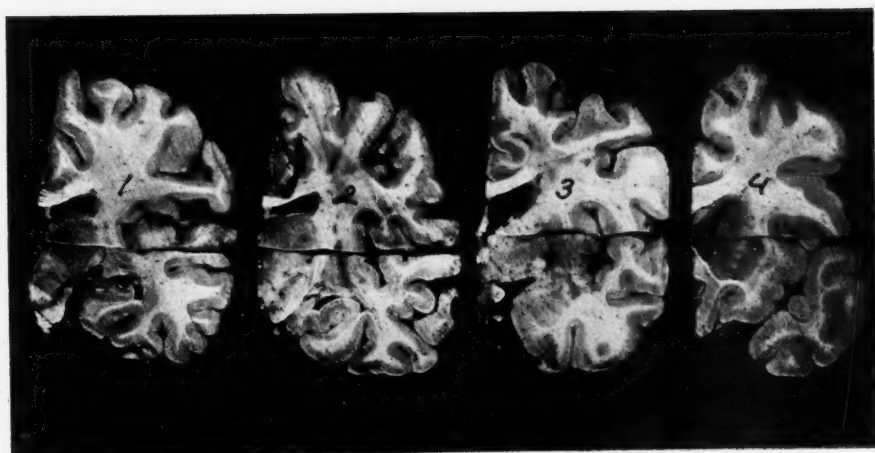


FIG. 8

DISTURBANCE OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD TO THE ALKALINE SIDE: ALKALAEMIA

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Introduction.

THE maintenance of a nearly constant reaction of the blood is essential for the preservation of health in the human body. The exact range of variation in reaction, which may be considered normal, is still in dispute, but probably lies between the reactions represented by pH 7.3 and pH 7.5. The normal reaction of the blood is therefore slightly alkaline. Under abnormal conditions much greater variations in the reaction may occur. Thus an acidity of pH 6.9 has been recorded by Cullen (1) in the blood of a patient dying from chronic nephritis, while in the reverse direction Grant and Goldman (2) have found a pH of 7.65, and Davies, Haldane, and Kennaway (26) a pH of 7.8, as the result of voluntary overbreathing. At these reactions symptoms of tetany sometimes supervened. In experiments on animals a temporary variation of the reaction of the blood to an alkalinity as great as pH 9.03 has been observed. In an extensive communication entitled 'Neutrality Regulations in the Body', Wilson (4) has recently reviewed our knowledge of the processes by which the body rids itself of excess acids and alkalis and maintains a relatively constant reaction of the blood and body fluids. The brief review of this subject given in the introduction to this paper has been based largely on his communication, and to it the reader is referred for a more detailed discussion of the processes involved.

In the normal oxidations of food materials, large amounts of carbonic acid and lesser amounts of phosphoric acid and sulphuric acid are constantly being produced. Muscular activity leads to lactic acid formation, and in certain pathological states large amounts of oxybutyric acid and diacetic acid may be formed. On the other hand, bases are constantly being taken with the food. The removal of excess acid and base is accomplished mainly by excretion, volatile acids being excreted by the lungs, and non-volatile acids and bases by the kidneys. In addition to excretion, removal of excess acid or base occurs by destruction, by conversion into a neutral substance, or one more easily excreted; thus ammonia is converted into urea, many organic acids are oxidized to carbonic acid, the kidneys produce ammonia to neutralize excess acid, and lactic acid may

be produced to neutralize excess base. Before these processes of excretion, or destruction, can be accomplished, acids and alkalis must be transported from their site of production in the cells, or absorption in the intestine, to the site where excretion or destruction takes place. This transportation must moreover be carried out without causing any marked change in the reaction of the body cells and fluids. This is made possible by the action of the buffers of the cells and body fluids, and especially the buffers of the blood. The most important of these buffers are haemoglobin and the phosphates and bicarbonates. When oxygen is given off to the tissues, oxyhaemoglobin is changed to the less acid substance, reduced haemoglobin. The content of the corpuscles tends therefore to become less acid, and a corresponding amount of carbonic acid can diffuse into the corpuscles from the tissues without changing their reaction. The reverse process occurs in the lungs, when reduced haemoglobin is changed into oxyhaemoglobin, and carbonic acid diffuses into the alveolar air. A further important mechanism in the transportation of carbonic acid is the phenomenon known as 'chloride shift'. When the blood is subjected to the increased tension of carbon dioxide, produced by the oxidations occurring in the body cells, large quantities of chlorine, and smaller amounts of other acid radicals, diffuse into the corpuscles, thus liberating base in the plasma which combines with the carbonic acid diffusing out from the tissues and forms bicarbonate. This process results not only in the transportation of a large part of the carbonic acid produced in the tissues, but leads to a great increase in the amount of plasma bicarbonate available for the neutralization of non-volatile acids. This is important, for in the case of non-volatile acids the neutralization and transportation is accomplished entirely by the bicarbonates, acids such as sulphuric and phosphoric combining with bicarbonate to form corresponding salts of those acids, and liberating carbon dioxide, which is excreted by the lungs. Bases, on the other hand, combine with carbonic acid to form their corresponding bicarbonate, and are transported as such to the kidneys, where the excess is excreted. Such is, in brief, the mechanism by which the body frees itself of excess acid and alkalis arising in the course of normal metabolism or produced in pathological conditions. The efficiency of the mechanism should finally be emphasized. By means of these delicately adjusted arrangements for transporting and eliminating acids, from 20 to 40 litres of normal acid are excreted daily by the lungs, while during the same period 50 to 150 c.c. of normal acid are eliminated by the kidneys. The lungs are therefore the main site of excretion of acid. The excretion of excess base is, on the other hand, carried out almost entirely by the kidneys. The rarity of alkali intoxication, when the kidneys are intact, proves the efficiency of the latter mechanism.

The methods for removal of excess acid and base are, we have seen, complex and multiple. The mechanism involved in the maintenance of the actual reaction of the blood is, however, simple and uniform. It consists in the maintenance of a constant proportion in the ratio of carbonic acid to bicarbonate in the plasma. If the former is increased without a corresponding increase in

the latter, the reaction of the blood becomes more acid; if the reverse occurs, the reaction is more alkaline.

Van Slyke (1) has pointed out that the following nine variations may occur in the acid-base equilibrium:

1. Uncompensated alkali excess: The bicarbonate is increased without a corresponding increase in carbonic acid, the pH is therefore increased; that is, the reaction of the blood is more alkaline.

2. Uncompensated CO_2 deficit: The carbonic acid is diminished without corresponding diminution of the bicarbonate (which may be either normal or actually diminished), the pH is therefore increased; that is, the reaction of the blood is more alkaline.

3. Compensated alkali excess: The bicarbonate is increased, but a corresponding increase of carbonic acid has also occurred, the pH therefore remains constant, the reaction of the blood is unchanged.

4. Compensated CO_2 deficit: The carbonic acid is diminished, but a corresponding diminution in bicarbonate has occurred, the pH therefore remains constant.

5. Normal acid-base equilibrium.

6. Compensated CO_2 excess: The carbonic acid is increased, but a corresponding increase has occurred in bicarbonate, the pH therefore remains constant.

7. Compensated alkali deficit: The bicarbonate is diminished, but a corresponding diminution in carbonic acid has occurred, the pH therefore remains constant.

8. Uncompensated CO_2 excess: The carbonic acid is increased without corresponding increase in the bicarbonate (which may be either normal or actually increased), the pH is therefore diminished; that is, the reaction of the blood is more acid.

9. Uncompensated alkali deficit: The bicarbonate is diminished without corresponding diminution of carbonic acid, the pH is therefore diminished; that is, the reaction of the blood is more acid.

In Table I these nine possible variations in acid-base equilibrium, the changes which occur in them, and the conditions known to give rise to them, are presented in tabular form.

Of the eight possible abnormal variations of acid-base equilibrium, all have been produced experimentally, and it is probable that most, if not all, may occur as pathological states in the human subject. The attention of the physician, studying disease in man, has been confined almost entirely to Nos. 7 and 9 in the above list—that is, compensated and uncompensated alkali deficit. These conditions occur most commonly as a complication of diabetes mellitus and of chronic nephritis, in the former due to the production of abnormal organic acids, the condition commonly designated ketosis, in the latter due to defective excretion of the non-volatile acids resulting from normal metabolism. The purpose of this communication is to show that the variations of acid-base equilibrium in the opposite direction equally merit the attention of the clinician,

and to report some examples of patients showing serious symptoms due, apparently, to increased alkalinity of the blood.

Case Reports.

Case I. L. H., No. 52384/21. A. W., male, aged 46.

An advanced case of chronic nephritis with high blood-pressure. Physical examination showed pallor, slight oedema, marked cardio-vascular hypertrophy with systolic blood-pressure of 235 and diastolic 150 mm. of mercury. There was a marked 'albuminuric retinitis'. There was headache, epistaxis, nausea and occasional vomiting, and a definite dyspnoea. The urine was somewhat diminished in volume, with fixed low specific gravity, contained a large amount of albumin, and on microscopic examination red blood cells and granular casts. There was well-marked nitrogen retention (blood urea = 0.141 per cent.), very deficient excretion of phenolsulphonaphthalein (trace in 2 hours), markedly diminished power of urea concentration (0.85 per cent. first hour, 1.1 per cent. second hour), and low diastatic index in the urine (D.I. plasma = 10, urine 3.3).

On July 4 the patient was put on large doses of sodium bicarbonate dr. vi daily for the purpose of observing the effect on renal excretion of reduction in acidity of the urine. The urine remained acid until July 8, and on July 10 became and remained definitely alkaline. On July 6, that is two days after starting the bicarbonate administration, the patient was not so well. There was shortness of breath, he complained of black spots before the eyes and was mentally depressed. These symptoms increased and reached a maximum on July 13, when there was very marked breathlessness and some wandering delirium. On this day the possibility of poisoning by bicarbonate was suspected and the drug discontinued. The following day, July 14, the patient was very much better, the breathlessness was much relieved, he slept better, and felt better in every way.

On July 15, the urine being neutral, sodium bicarbonate dr. iii daily was resumed. The urine again became strongly alkaline and symptoms rapidly returned. Dyspnoea, black spots before the eyes, delusions, insomnia, and irritability were prominent symptoms. Signs of tetany were not noted. On July 18 bicarbonate was discontinued, by the 19th the patient was much improved, and on the 20th was quite himself again.

Unfortunately, at the time this patient was observed, estimations of the hydrogen-ion concentration of the plasma were not being made, so that no figures for this are available, and we must depend on the estimations of plasma bicarbonate for our conception of the changes occurring in the blood. On July 12, the day preceding the day of maximum symptoms in the first attack, the plasma bicarbonate was 94, a figure indicating a marked alkali excess. On July 21, three days after bicarbonate was finally discontinued, and although all symptoms had disappeared, the bicarbonate of the plasma was 86. In the absence of estimations of hydrogen-ion concentration it is impossible to know the reaction of the blood, but it seems probable at the time of the first examination, on July 12, when marked symptoms were present and the plasma bicarbonate was 94, that CO_2 retention had failed to maintain the $\text{H}_2\text{CO}_3:\text{BHCO}_3$ ratio, and that the reaction had therefore become more alkaline—a condition of uncompensated alkali excess or, in one word, alkalaemia. The complete absence of symptoms on July 22 suggests that in spite of the high plasma bicarbonate, which was then 84, retention of CO_2 sufficient to maintain the ratio was occurring, thus keeping the reaction of the plasma within normal limits; in other words, the alkali excess had now become compensated.

We see then in this patient certain symptoms produced by sodium bicarbonate due, we believe, to an upset of the normal acid-base equilibrium.

It is probable that in this individual the underlying cause of the intoxication was the inadequate renal excretion leading to accumulation of the sodium bicarbonate administered. That this is the case is strongly supported by the observation that the urine of July 7, twenty-four hours after the appearance of symptoms, was still strongly acid with a pH of 6.6.

Case II. L. H., No. 20537/22. L. B., female, aged 27.

The patient was in the eighth month of pregnancy. She was admitted complaining of pain in the right hypochondrium, radiating to the back, and accompanied by vomiting. For eleven years she had suffered, especially during the winter months, from gnawing pain in the right hypochondrium, coming on from five minutes to one hour after meals and relieved by taking alkalis. The pain until recently had never been acute. There had been no vomiting, no jaundice, and no haematemesis or melaena. Four months before admission the patient had an attack of severe, colicky, spasmodic pain lasting four hours. Since that time her condition had become steadily worse, and for two weeks before admission she had been having one or two attacks of pain a day. Vomiting had accompanied the attacks. Between the attacks she had been quite free from pain. There were no urinary symptoms. Examination showed an enlarged uterus, the fundus half-way between umbilicus and ensiform. Active foetal movements were noted. There was tenderness and rigidity in the right hypochondrium. On February 16 the patient vomited blood. On February 18 she was seen by Mr. A. J. Walton, who diagnosed gall-stones with multiple acute gastric erosions. Labour was induced by the aid of bougies on the afternoon of February 18, and a dead child delivered in the early hours of the morning of the 19th. Further haematemesis occurred during labour. Following delivery, her condition was much improved, but on February 20 a further haematemesis occurred. Vomiting persisted on February 21 and 22, and on this date, as the patient was drowsy and difficult to rouse, an acidosis was suspected and she was given sodium bicarbonate and glucose injections intravenously and per rectum. The sodium bicarbonate was given in 2½ per cent. solution, of which she received the following:

February 22.	2-30 p.m., oz. xx (600 c.c.) intravenous.
	9-30 p.m., oz. xx (600 c.c.) intravenous.
February 23.	2-30 a.m., oz. x (300 c.c.) per rectum.
	6.30 a.m., oz. x (300 c.c.) per rectum.
	10-30 a.m., oz. x (300 c.c.) per rectum.

Immediately following the second intravenous injection twitching movements of the fingers, legs, and lips were noticed, and an hour later occasional twitching movements of the arms. She was unconscious and motionless, lying perfectly still except for respiratory movements. About 3 a.m. of the 23rd she became restless for an hour, and then again became absolutely quiet and motionless. Respiration on the morning of the 23rd became much slowed, and at 8 a.m. was only 9 per minute, breathing being noted as heavy but not stertorous and depth as very variable. By noon the rate had again risen to 20.

The patient was first seen by the writer at 2.30 p.m. on February 23; she was comatose, but groaned faintly when roused. There was marked pallor, with dark sunken eyes, the mouth was held open, the tongue was brown, dry, and furred. There was definite tetany with markedly increased muscular irritability. The head was retracted, but there was no rigidity of the neck; there were occasional twitching movements of the face. There was carpal spasm with the fingers flexed over the thumbs. The feet were extended, and the left especially was hypertonic. The pupils were very contracted, equal, and reacted to light. The pulse was rapid, fairly full, but soft and easily compressible. The systolic

blood-pressure was 95 mm. of mercury and the diastolic 55. The respirations were rapid and deep, about 45 to the minute. The plasma bicarbonate at 3.30 p.m. was 101. Unconsciousness deepened, the respirations gradually slowed, and patient died at 6 p.m. Unfortunately permission for a post-mortem was not obtained. Analysis of blood taken at 3.30 p.m. on February 23 yielded the following results:

Plasma bicarbonate	101 ¹
Plasma chlorides	0.53 per cent.
Serum calcium	0.010 per cent.
Plasma sodium	0.38 per cent.
Blood urea	0.130 per cent.

That is, the plasma bicarbonate, plasma sodium, and blood urea were all markedly increased, the plasma chlorides were definitely diminished, and the serum calcium was normal. This case is apparently an example of overdosing with sodium bicarbonate, an exaggeration of the condition present in Case I.

Case III. L. H., No. 34048/23. M. H., male, aged 47.

A case of carcinomatous obstruction of the pylorus. Patient stated that he was perfectly well until two weeks before admission on December 15, 1923, when he began to have abdominal pain and vomiting. The pain was to the right of the umbilicus, came on about five hours after a meal, and was relieved by vomiting. There had been much gaseous eructation, and vomiting had occurred from six to seven times daily, usually four to five hours after food. There had been no haematemesis and no melaena. The appetite had been good till two weeks before admission; since then there had been no desire for food. He said that he had lost 17 lb. in weight in the three weeks before admission. On examination, a dilated stomach could be seen bulging the abdominal wall, there was visible peristalsis, and a very marked succussion splash. There was deep tenderness between the umbilicus and the right costal margin, and in this region an indefinite mass could be felt. The examination of the heart, lungs, and central nervous system was negative. The stomach was washed out on December 17, 18, and 19, a large amount of foul, turbid fluid being removed. Carpo-pedal spasms were first noted on December 18; they occurred spontaneously, but were also evoked by handling or moving the patient. There were no spasms of the facial muscles. During the night of the 18th-19th, two generalized convulsions occurred, in which the left side was especially affected. The patient was first seen by the writer on December 20. He was desperately ill, cyanosed, with sunken eyes, open mouth, and dazed, staring expression. The tongue was dry and furred. There was great mental confusion and at times complete unconsciousness. Carpo-pedal spasms occurred at intervals, there was greatly increased muscular irritability, but Chvostek's sign was absent. Divergent squint was noticeable at times. There was no facial weakness. The pupils were normal, the fundi negative, the tendon reflexes brisker on the left side than on the right. Patient had passed no urine for twenty-four hours, but there was no evidence of retention. During the day the respiration became at times very feeble, but no complete apnoea occurred. During the attacks of partial apnoea, the face became ashen, the pulse rapid and feeble, and patient appeared moribund. This condition would last for from one to two minutes, respiration would then improve, and the patient gradually recover. Examination of the blood showed an uncompensated alkali excess, the plasma pH 7.6, bicarbonate 119. At 3.15 p.m. 1 gm. of calcium chloride in 30 c.c. of water was given intravenously. This was followed within half an hour by a marked reduction in muscular irritability, which, however, still remained greater than normal. At 4 p.m. oz. x of 2 per cent. ammonium chloride were given per rectum, and this amount was repeated three-hourly until two pints had been

¹ This figure is probably too low. See foot-note to Table II.

given; this was mostly retained, not more than oz. x being returned. At 5 p.m. and again at 10 p.m. 450 c.c. of normal saline were given intravenously. During the night patient passed 450 c.c. of urine. The following morning, December 21, patient seemed better, but an acute parotitis had developed. His mental condition was clearer, no further convulsions had occurred, there were no carpo-pedal spasms, and the muscular irritability was diminished. The plasma pH was 7.4, the bicarbonate 75. He was given 300 c.c. of 5 per cent. glucose in normal saline at 12 noon, and at 1.30 p.m. Mr. Sherren operated, and found an inoperable carcinoma of the lesser curve of the stomach involving the pylorus. Gastro-enterostomy was performed. The following day, December 22, the patient was completely conscious, and seemed a little better, but the pulse remained rapid and weak. There was no evidence of tetany and no further convulsions occurred. On the evening of December 22 he vomited once, his temperature rose sharply to 103.2° F. during the early hours of December 23, and he died before morning.

Analyses of the blood and urine in this patient gave the following results:

	20.12.23.	21.12.23.
pH	= 7.6	7.4.
Plasma bicarbonate	= 119	75.0.
Plasma chlorides	= 0.295 per cent.	0.49 per cent.
Blood urea	= 0.265 per cent.	
Plasma phosphorus	= 0.0075 per cent.	
Plasma sodium	= 0.325 per cent.	0.32 per cent.
Serum calcium	= 0.011 per cent.	0.011 per cent.

That is, on the 20th the alkalinity of the blood was increased, the plasma bicarbonate, blood urea, and plasma phosphorus all increased, the plasma chlorides were markedly diminished, the plasma sodium and serum calcium were normal. On the following day, some 16 gm. of ammonium chloride per rectum and some 10 gm. of sodium chloride intravenously having been given in the interval, the reaction of the blood and the plasma bicarbonate were normal and the chlorides markedly increased, though still below the amount normally present in plasma.

The urine passed during the night of the 20th-21st showed on analysis:

pH	= 5.6.
Ammonia	= 22 c.c. N/10 in 100 c.c.
Titrateable acid	= 24 c.c. N/10 in 100 c.c.
Chlorides	= Trace.
Organic acids	= 68 c.c. N/10 in 100 c.c.
Phosphorus	= 0.036 per cent.

We have then the curious anomaly of the excretion of a quite highly acid urine by a patient with an over-alkaline plasma, the acidity of the urine being apparently due to organic acids. The same phenomenon will be noticed in the next case to be reported. Acetone bodies were present in the urine. In the two previous cases the cause of the alkaline excess was overdosing with sodium bicarbonate; this patient illustrates the disturbance of acid-base equilibrium resulting from pyloric and duodenal obstruction and leading to the clinical condition of gastric tetany.

Case IV. L. H., No. 30352/24. F. S., male, aged 28.

He had been perfectly well until three weeks before his admission to the London Hospital on January 29, 1924. His illness began suddenly with diarrhoea, lasting one day, and pain in the right side of the chest. He went to bed and was seen by a doctor, who diagnosed pleurisy. He was in bed for about two weeks, gradually improved, and got up. After being up and about the house for one or two days he suddenly began to vomit on January 26, and vomited persistently

until admission. His mother stated that he had vomited large quantities, 'wash-basins full', and that she had noticed that he vomited more fluid than he was given. No history of previous illness could be elicited. On admission, he was obviously extremely ill. The cheeks were flushed, the lips and ears deeply cyanotic, the eyes sunken, the facies hippocratic. The skin was dry and the extremities cold. His temperature was subnormal. Mentally, he was dull and unable to give an account of his illness. Vomiting occurred frequently, sometimes green bile-stained, sometimes brownish in colour. The tongue was moist, but covered with a thick brown coating. The abdomen was distended, except in the right upper quadrant, by an enormously dilated stomach, the lesser curve of which was visible at the level of the umbilicus, the greater curve reaching almost to the symphysis. Loud splashing was easily elicited, coin-bell sound was readily evoked all over the swelling, which was tympanitic on percussion, except in the left flank. The right upper quadrant of the abdomen was flattened. No other tumour was felt in the abdomen, but there was some tenderness to deep pressure in the right hypochondrium. Faeces were passed shortly after admission. There was diminished expansion of the right chest, and diminished tactile vocal fremitus, diminished resonance on percussion, and diminished breath-sounds at the base of the right lung posteriorly. The heart was displaced to the right, the apex-beat in the 5th space only $2\frac{1}{2}$ in. from the mid-line—that is, about 1 in. to the left of the sternum. The heart-sounds were normal in all areas, and there were no adventitious sounds. The pulse, on admission, was 80 to the minute, regular, and of good volume. There was a slight convergent squint, the tendon reflexes were normally active and equal on the two sides. There was markedly increased muscular irritability, Chvostek's sign was absent. Patient stated that he had passed very little urine since the onset of vomiting, and that he had not voided more than an ounce of urine at a time. Catheterization yielded only some 1 c.c. of clear urine, which showed on examination a few leucocytes and red blood cells and a considerable amount of albumin. The case was considered one of duodenal obstruction, with dilated stomach and resulting alkalaemia. Because of the marked displacement of the heart to the side of the pulmonary lesion, the latter was thought to be massive collapse of the lower lobe of the right lung, due to the intra-abdominal condition. The plasma pH was 7.6, the plasma bicarbonate 106, the plasma chlorides 0.39 per cent.; the blood urea was 0.132 per cent.

The foot of the bed was raised, and the patient turned on his face; he was, however, unable to remain in this position for long. At 7 p.m., on January 29, ammonium chloride was given per rectum, but very little was retained. At 8 p.m. a stomach-tube was passed and 1,400 c.c. of brown fluid siphoned off, the stomach was washed with tap-water. At 8.45 p.m. 450 c.c. of 5 per cent. glucose in normal salt solution were given intravenously and 150 c.c. of the same solution subcutaneously. At 9.30 p.m. the patient became collapsed, with rapid, feeble pulse and cold extremities; the respirations were 50 to the minute and very shallow. The collapse was attributed to the effects on the circulation of the removal of fluid and gas from the stomach. The application of a pad and tight binder to the abdomen was followed by rapid improvement. At 11.45 p.m. 750 c.c. of normal saline were given intravenously. Ammonium chloride was given per rectum at four-hourly intervals throughout the night, but little was retained. On the morning of January 30 the patient seemed definitely improved; he looked brighter, and said he felt better. He had not vomited since his stomach had been washed out. His pulse was good, his extremities warm, his respiration normal. The muscular irritability had disappeared. At 11.45 a.m. 650 c.c. of 2.5 per cent. glucose in normal saline were given intravenously, and at 1.30 p.m. the abdomen was opened by Mr. Perrin under ether anaesthesia. The stomach and duodenum up to the site of crossing of the mesenteric vessels were dilated and intensely congested. No obstruction or cause for the dilatation was discovered. Posterior gastro-jejunostomy was performed. On January 31, the day following operation,

the patient's condition was only fairly satisfactory; he was cyanosed and dyspnoeic, coarse moist râles and rhonchi were audible over both sides of the chest. His condition gradually grew worse, dyspnoea became more marked, the lung signs increased in intensity, and he died on February 2 at 11 p.m.

Analysis of the blood taken on the morning of February 2 showed:

Plasma pH	= 7.43.
Plasma bicarbonate	= 56.0.
Plasma chlorides	= 0.63 per cent.
Blood urea	= 0.191 per cent.

It will be seen that the reaction of the blood, the plasma bicarbonate, and the plasma chlorides had returned to normal, but that the blood urea still remained high.

Post-mortem examination showed operation gastro-jejunostomy for dilatation of the stomach, broncho-pneumonia, chronic right empyema, chronic abscesses in lungs and left kidney, staphylococcal pyaemia.

This patient showed the chemical changes in the blood which are apparently characteristic of a high intestinal obstruction. There was a marked diminution in the plasma chlorides, a great increase in the plasma bicarbonate, an increase in the alkalinity of the blood, and a great increase in the blood urea. Reference to Table II will show that in this patient the same curious paradox is presented that was noticed in the previous case, namely, the passage of a strongly acid urine during the period of recovery from a severe alkalaemia. In this case also acetone bodies were present in the urine, showing again the fallacy of considering Ketonuria as indicative of acidaemia.

Case V. L. H., No. 30557/24. S. G., male, aged 47.

Admitted to the London Hospital February 13, 1924. This case is included in the series because, although no disturbance of acid-base equilibrium was demonstrated, certain clinical and chemical changes were noted which would seem to relate it to the cases previously reported. In the light of our present rudimentary knowledge of these changes it would seem advisable to place on record any data which may possibly lead to a solution of the problems.

The patient was perfectly well until seven days before admission, when he was seized with sudden abdominal pain and vomiting. He vomited seven or eight times during the first night and had frequent vomiting of large quantities of fluid for the next five days. He could keep nothing down, and would vomit a chamberful at a time. During these five days patient was completely constipated in spite of taking oz. iv of castor oil in divided doses. For three days before admission there had been three to four fluid stools daily, and for two days before admission no vomiting had occurred. The patient stated that he had lost a great deal of weight. He was said to have passed very little urine and only small quantities at a time; he had been delirious occasionally. At the beginning of the illness he appeared feverish, but this passed off in a day or two.

On admission the patient was obviously very ill, with pinched cheeks and sunken eyes. He was perfectly clear mentally, but speech was husky and difficult, on account of the dryness of his throat. The tongue was dry and covered with brown fur. His temperature was 96° F., pulse 114, and respirations 26. There was definite hyperpnoea. There was a slight generalized oedema, most marked over the anterior abdominal wall. The abdomen was distended, except the right upper quadrant, which was comparatively flattened. Visible peristalsis from left to right was occasionally seen in the upper abdomen. A loud succussion splash was easily elicited. The abdomen was tympanitic on percussion, with shifting dullness in both flanks. There was musical splashing and coin-bell

sound on auscultation over the distended abdomen. Rectal examination showed ballooning of the rectum, but nothing else abnormal. The heart was displaced to the right, the apex-beat $2\frac{3}{4}$ in. to the left of the mid-sternal line; stomach tympany extended to the level of the 3rd rib on the left side. There was well-marked muscular irritability, but no carpo-pedal spasm. Chvostek's sign was absent. Analysis of blood, taken at 3.30 p.m. 13.2.24, showed:

Plasma pH	= 7.43.
Plasma bicarbonate	= 51.
Plasma chlorides	= 0.478 per cent.
Blood urea	= 0.276 per cent.

It will be seen that though no alkalaemia was present in this patient, increased muscular irritability was noticed, and that his blood showed the same low content of plasma chlorides and high content of blood urea seen in the other cases.

The patient was given 600 c.c. of normal saline intravenously, and a Rehfuess tube was passed and 450 c.c. of sour greenish fluid aspirated from his stomach. The following morning, February 14, the patient seemed definitely better: temperature 97° F., pulse 80, respirations 22. At 11.30 a.m. 600 c.c. of normal saline were given intravenously, and at 3.30 p.m. the stomach was washed out with tap-water. At 5 p.m. he complained of sudden severe right-sided abdominal pain. This persisted, and there was right-sided abdominal rigidity. Laparotomy at 11 p.m. revealed an abdomen full of thick foul pus, and an old perforation of a gangrenous appendix. The patient died four hours after the operation.

Microscopic Examination of Kidneys. (Prof. H. M. Turnbull.)

'In the cortex there are a few small areas in which the interstitial tissue at the side of the interlobular vessels is increased in amount and is dense. Such areas contain a fibrotic glomerulus or a group of atrophied tubules, or both together. The general pattern of the cortex is not disturbed. The media of the renal vessels is not hypertrophied, and there is neither hypertrophy nor degeneration of the intima. The veins are conspicuously engorged.

'The epithelium lining Bowman's capsule, near the efferent tubule, is occasionally swollen and granular. The cytoplasm of the cells lining the first convoluted tubules is conspicuously granular, and occasional nuclei show karyolysis. The cells lining the descending limbs of the loops of Henle occasionally show large fatty granules close to the nucleus. The cells of the ascending limbs of Henle contain many small granules of fat. Slightly larger, fatty granules are scattered throughout the cytoplasm of the epithelium of the second convoluted tubules.

'The lumina of the first convoluted tubules contain albuminous granules and threads. There are hyaline casts in many of the ascending and descending limbs of the loops of Henle and in many of the collecting tubules, and a less number in the discharging tubules. A few of the descending limbs of the loops of Henle contain granular, fatty casts; a very few of the descending limbs contain granular casts which are not fatty.

'The fat in the epithelium and in the granular casts is isotropic.'

Summary and Interpretation. (Prof. H. M. Turnbull.)

'The kidneys on microscopic examination show an amount of "chronic interstitial nephritis" which is only slightly greater than that found in almost all subjects over forty years of age. The tubules show moderate albuminous degeneration and slight fatty degeneration. There are a few fatty casts and numerous hyaline casts. The fatty casts may possibly be connected with the fibrotic

omeruli, but the hyaline casts are much too numerous to have such a connexion; they are clearly associated with the parenchymatous degeneration. The number of hyaline casts is remarkable in view of the relatively slight degree of parenchymatous degeneration.'

Discussion.

Four cases of alkalaemia are reported, two due to overdosing with sodium bicarbonate, and two due to a high intestinal obstruction. A fifth case of low intestinal obstruction is added for comparison. The results of chemical investigations of the blood and urine of these five cases are given in Table II.

It is obvious that the disturbance of acid-base equilibrium in these four patients results from two quite different processes. It would seem advisable therefore first to discuss these two groups separately, and then to see if any common symptoms occur which can justly be attributed to the resultant alkalaemia, and if any common manifestations can be determined which may shed more light on the underlying processes.

Toxic effects from sodium bicarbonate have been noted by a number of observers. In 1913 Blum (5) reported the occurrence of convulsions from the intravenous injection of sodium bicarbonate in patients with diabetic coma. Howland and Marriott (6) have seen tetany result in three cases in infants with acidosis under treatment with sodium bicarbonate. Harrop (7) saw tetany develop during an intravenous injection of sodium bicarbonate in a patient with bichloride of mercury poisoning. Healy (8) has reported six cases of tetany, four of which were fatal, occurring in patients given huge doses of sodium bicarbonate per rectum after operations. MacCallum (9) and his associates have produced apathy, twitching, convulsions, and coma, in dogs by the intravenous injection of sodium bicarbonate and sodium carbonate. Hardt and Rivers (10) have reported unpleasant symptoms, sometimes of great severity, and accompanied by changes in the acid-base equilibrium, in patients undergoing intensive alkali medication for gastric and duodenal ulcer. They particularly emphasize that such complications are more likely to occur, and show a greater severity, in patients suffering from renal disease. It will be noted that Harrop's patient had badly damaged kidneys, and that the cases of Howland and Marriott were infants suffering from acidosis as a result of deficient kidney excretion. Deficient renal excretion would seem therefore to play an important part in cases of poisoning by sodium bicarbonate. It was present in Case I of this series, in which poisoning resulted from a dosage of bicarbonate no greater than is often employed in the treatment of various conditions. Reference to Table II will show that in Case II the blood urea was also high, and it might readily be assumed that here too deficient renal excretion was present. As will be pointed out later, a high blood urea cannot however be taken by itself as establishing a kidney lesion, and no other evidence of deficient excretion was present in this case.

The changes in the blood which result from overdosing with sodium bicarbonate consist primarily in an increase in the bicarbonate of the plasma

Compensating retention of carbon dioxide occurs for a time, but this eventually fails and the pH of the blood then becomes increased. The other changes which may occur are as yet not clear. It will be seen that in both our cases there was an apparent diminution in plasma chlorides. It should be remembered, however, that Case I was a patient with chronic nephritis, a condition in which the plasma chlorides are often diminished, and that Case II had been vomiting. Only two references to the plasma chlorides in bicarbonate intoxication have been found—one patient of Hardt and Rivers, and one dog of MacCullum's; in both the plasma chlorides were normal. Gamble, Ross, and Tisdall (11) have shown that there is a regulatory mechanism of the body which tends to keep the amount of fixed base in the blood constant, so that if the salts of other acids are present in increased quantity in the blood a migration of sodium chloride into the tissues occurs, leaving the fixed base relatively constant. With an increase in the plasma bicarbonate one would expect therefore a fall in the plasma chlorides. There is some evidence of such a mechanism in Case I, in which in spite of the increase in bicarbonate no increase of sodium in the plasma is demonstrable. In Case II, however, in which very large doses of bicarbonate were given, an actual increase of sodium in the plasma occurred. The presence of a high blood urea in both our cases requires explanation. It has been already pointed out that bicarbonate intoxication has usually been noted in patients with damaged renal excretion, and in these a high blood urea would be expected. An example is Case I, in which the occurrence of a high blood urea is adequately explained by the existing chronic nephritis. Case II is more difficult of explanation, for in this patient there was no other evidence of a renal lesion. In the experimental investigations of bicarbonate intoxication no figures for blood urea are given, and there is therefore no evidence as to the possible effect of this intoxication on the urea content of the blood. *A priori* none would be expected, but in the light of the findings in this patient the question would appear to merit investigation. There is another explanation, however, which must be considered. As will be shown later, a high blood urea is usually present in cases of pyloric and intestinal obstruction, and in Case II the diagnosis of gall-stones and acute gastric erosion may have been incorrect, and the patient really suffering from one of these conditions. A perusal of the history of this case will show that such an explanation, though not considered at the time, is by no means impossible.

The symptoms of poisoning by sodium bicarbonate as given by Hardt and Rivers (10) are in agreement with those noted in these cases. The patients are unduly introspective and nervous. They are irritable and complain of trifles. There is headache, nausea and vomiting, dizziness, vertigo, and light-headedness. They may complain of aching pains in the muscles and joints. There is weakness, followed by absolute prostration. They become apathetic, drowsy, and are roused with difficulty, and finally tetany and convulsions may supervene. In Case I there was breathlessness and air-hunger. Case II was *in extremis*; the respirations were noted as rapid and deep.

The disturbance of acid-base equilibrium resulting from high intestinal

obstruction was first demonstrated by McCann (12), who showed that following operations on the stomach, which exclude acid from the duodenum, tetany may develop, accompanied by an increased bicarbonate content of the plasma. Similar results were obtained by ligation of the pylorus in dogs by MacCallum (9) and his associates, and by Hastings, Murray, and Murray (13). MacCallum pointed out that the rise in plasma bicarbonate was associated with a fall in the plasma chlorides, and that if this fall in chlorides was prevented by the continuous injection of sodium chloride into the duodenum beyond the site of obstruction, no rise in bicarbonate occurred. He considered the primary disturbance to be the loss of hydrochloric acid from vomiting. This he thought led to a depletion of chlorine in the plasma, thereby liberating bases which combined with carbonic acid to form bicarbonate, the increase so caused eventually producing an alkalaemia.

The occurrence of tetany in some cases of dilated stomach has long been known to clinicians, and has gained recognition under the title 'gastric tetany'. Until recently no satisfactory explanation of its origin has been forthcoming. The finding by Grant (14) of a marked increase in the plasma bicarbonate in two patients with this condition, and the demonstration of a severe alkalaemia in Case III of this series, a typical example of gastric tetany, corroborate the findings of experimental investigations in animals, and suggest that the tetany in these cases is a symptom of alkalaemia, comparable to that occurring in poisoning with sodium bicarbonate. It has been already shown that the fundamental change in the inorganic constituents of the blood of dogs with pyloric obstruction, which leads to this disturbance of acid-base equilibrium, is a fall in the plasma chlorides. This is seemingly also true for gastric tetany in man, Case III in this series and the single patient investigated by Grant both showing a marked diminution of plasma chlorides. Brown, Eusterman, Hartman, and Rowntree (16), have also observed this early depletion of chlorides in pyloric and duodenal obstruction in man, and Haden and Orr (15) have demonstrated that a similar fall in the blood chlorides is the first change in the chemistry of the blood of dogs in which any part of the intestine has been obstructed. They have called attention to the low blood chlorides in intestinal obstruction in man (22). Case IV in this series illustrates the depletion of chlorides in a case of duodenal obstruction, and Case V a diminution of plasma chlorides in a patient with ileus following perforation of the appendix, in this instance unaccompanied by any alteration of acid-base equilibrium.

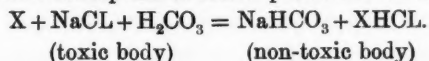
The theory of MacCallum (9) that the diminution in plasma chlorides is due to a loss of hydrochloric acid in the vomit has been widely accepted. Clinical evidence is however against it, for gastric tetany is known to occur in patients with carcinomatous obstruction of the pylorus, a condition in which there is usually no free hydrochloric acid in the gastric juice. Case III of this series is a typical example. This patient had tetany, a definite alkalaemia and the plasma chlorides were the lowest met with in this series. He had a carcinomatous obstruction of the pylorus, and there was no free hydrochloric

acid in the vomitus. Haden and Orr (15) have seen the fall in chlorides in a patient in whom there was no vomiting, and state that in dogs with experimental intestinal obstruction the fall in plasma chlorides occurs before the onset of vomiting, and may be marked in cases in which the loss of chloride in the vomitus is negligible. They have also shown that a similar diminution in chlorides occurs in intestinal obstruction in the rabbit, an animal in which vomiting does not occur. The diminution in plasma chlorides which follows pyloric and intestinal obstruction is therefore, almost certainly, not entirely due to a loss of hydrochloric acid in the vomitus.

This conclusion brings us to a consideration of the other changes in the chemistry of the blood which are found in intestinal obstruction. It will be noted that Case III, pyloric obstruction, Case IV, duodenal obstruction, and Case V, general ileus, all show a high blood urea. The occurrence of a high blood urea in intestinal obstruction was observed first by Tileston and Comfort (17). Their observation has been confirmed by Rabinowitch (18) and Louria (19), who have emphasized the value of the determination of blood nitrogen in the diagnosis and prognosis of acute abdominal conditions. Cooke, Rodenbaugh, and Whipple (20) have studied the blood nitrogen in experimental intestinal obstruction in dogs; they consider the increase to be due to an increased destruction of body protein resulting from the intoxication. Brown, Eusterman, Hartman, and Rowntree (16), on the other hand, consider that the increased blood urea is due to deficient excretion by the kidneys, and think that the symptoms, especially the mental aberration, are uraemic. They have described what they call a toxic nephritis in patients with duodenal and pyloric obstruction, and report the gross and microscopic appearance of the kidneys in six fatal cases. Their paper is not altogether convincing, but some confirmation of their view is found in our cases, for it will be noticed that in spite of a very high concentration of urea in the blood the urea in the urine was low in all three cases. In two the figures are striking. This low concentration of urea in the urine could not have been due to dilution, as these patients were all passing only small amounts of urine. It certainly suggests that in these patients renal efficiency was seriously impaired.

The interpretation of the significance of the rise in blood urea is further complicated by the work of Haden and Orr (23), who have shown that the rise in non-protein nitrogen of the blood does not occur until there is a marked depletion of the chlorides. They have shown that if the fall of plasma chlorides is prevented no rise in non-protein nitrogen or of plasma bicarbonate occurs, and no symptoms of toxæmia develop. They have succeeded, by the use of large subcutaneous injections of sodium chloride, in keeping dogs with intestinal obstruction alive, and free from symptoms, for periods up to twenty-eight days. They have shown that only sodium chloride has this effect, and that glucose and other salts such as phosphates, bicarbonates, &c., are useless for this purpose. They believe that the primary toxic substance produced in intestinal obstruction is one with a marked destructive action on protein, and that the symptoms of

intoxication which we associate with that condition are due to the resultant split products. They believe that the chlorides, if present in sufficient concentration, prevent in some way this tissue break-down, and that the depletion of blood chlorides is a protective mechanism. They suggest the following equation as one possible conception of such a protective mechanism:



Whatever the method of action may be, the experiments of Haden and Orr would seem to demonstrate the importance of sodium chloride in combating the intoxication of intestinal obstruction, and in preventing the resultant rise in blood urea and disturbance of acid-base equilibrium.

From the foregoing it would seem to be established that the alkalaemia of pyloric and intestinal obstruction is a secondary change depending on the chloride depletion. In bicarbonate poisoning, on the other hand, the increase in plasma bicarbonate and resulting alkalaemia is primary, and chloride depletion, if it occurs, a secondary phenomenon. The symptoms of alkalaemia in man are still uncertain, although those noticed in poisoning by sodium bicarbonate have been given. In pyloric and high intestinal obstruction the general symptoms are so severe that minor symptoms due to the alkalaemia might well be overshadowed. The occurrence of tetany in both groups is of interest, and would seem to relate this symptom at least directly to alkalaemia. Morris (24) has shown that the tetany of alkalaemia is probably due to anoxaemia. He has shown that in alkalaemia there is not only diminished oxygenation of the arterial blood, but that the amount of oxygen given off to the tissues is greatly diminished. He found that any condition which led to anoxaemia caused also an increased electrical excitability of the neuromyone. Koehler (25) has seen dyspnoea, cyanosis, and mental confusion disappear coincidentally with recovery from alkalaemia, and has suggested that these may be due to anoxaemia. He has suggested that the cause of anoxaemia in alkalaemia is a disturbance of the normal shift of the chlorine ion between plasma and corpuscle with a resulting stabilization of the haemoglobin-chloride combination.

A survey of the symptoms we have described as occurring in alkalaemia reveals their similarity to those of anoxaemia. It would seem probable that this is their real explanation. In Case I, in which on two occasions we were able to watch the gradual onset of an alkaline intoxication, breathlessness was one of the earliest and most distressing symptoms. Cyanosis was well marked in the cases of pyloric and duodenal obstruction, and it has been particularly emphasized by Brown, Eusterman, Hartman, and Rowntree (16), who speak of the 'red facies' which they consider to be due to dehydration. The mental aberration, dizziness and vertigo, the increased muscular excitability, and muscular cramps, are all in keeping with anoxaemia as the underlying cause. In this anoxaemia may lie also the explanation of the acetonuria which occurs in alkalaemia. Acetonuria occurred in both patients in this series in which its presence was looked for (Cases III and IV). For long the occurrence of

acetonuria was the most widely used popular test for the presence of acidaemia, but Davies, Haldane, and Kennaway (26) showed in 1920 that acetonuria resulted also from the administration of large doses of sodium bicarbonate, and MacAdam and Gordon (27) have reported its occurrence in alkalaemia. The cause of acetonuria is believed to be diminished oxidation, and the cause of its usual occurrence is the absence of essential carbohydrate. I would suggest that in alkalaemia the diminished oxidation may result from the accompanying anoxaemia.

If the theory that the symptoms of alkalaemia depend on anoxaemia be correct its importance in the study of disease in man is obvious. An adequate supply of oxygen is the most essential requisite of the body cells, and anything which may interfere with it must be of prime importance. In this paper only examples of alkalaemia due to alkali excess are presented, but the alkalaemia due to carbon dioxide deficit also has clinical importance. In various conditions overbreathing is a common symptom, and whenever this occurs alkalaemia may result. Fraser, Ross, and Dreyer (28) have demonstrated the occurrence of such an alkalaemia in patients with cardiac failure, an observation repeatedly confirmed in our wards. The evidence submitted in this paper would seem indeed to suggest that of the two directions of disturbance of acid-base equilibrium, that towards the alkaline side may well be of greater clinical importance than the more widely appreciated disturbance in the acid direction.

Summary.

The mechanism by which the body frees itself of excess acids and alkalis while maintaining a relatively constant reaction of the blood, and the possible variations in acid-base equilibrium which may occur, are reviewed. Four cases are reported illustrating two modes of origin of alkalaemia—overdosing with sodium bicarbonate, and pyloric and high intestinal obstruction. A case of low intestinal obstruction is added for comparison. The changes in the chemistry of the blood in the two conditions are discussed. In the cases reported the changes in the blood were remarkably similar—an increase of the pH of the plasma, of the plasma bicarbonate, and of the urea content of the blood, and a diminution of the plasma chlorides. It is shown that these changes are characteristic of pyloric and high intestinal obstruction, but that in the patients with bicarbonate intoxication the changes found in the plasma chlorides and in the blood urea were open to other explanations and that their occurrence in these patients may have been accidental. Clinical evidence against the theory that the alkalaemia of pyloric obstruction and the resulting condition of gastric tetany are due to loss of hydrochloric acid in the vomitus is submitted. The views of Haden and Orr on the nature of the intoxication occurring in intestinal obstruction are reviewed. The symptoms of alkalaemia are recorded, and the probability of their dependence on anoxaemia is discussed. The theory is advanced that the ketonuria of alkalaemia is due to anoxaemia. The opinion

is expressed that the disturbance of the acid-base equilibrium to the alkaline side may well prove more important in disease in man, than those in the opposite direction which have hitherto received our almost exclusive attention. The successful treatment of alkalaemia by the administration of ammonium chloride per rectum is reported.

To Dr. J. R. Marrack, who is responsible for the chemical determinations listed in Table II, my warmest thanks are due, not only for this assistance, but also for valuable advice regarding the preparation of this paper.

TABLE I. *Variations of Acid-base Equilibrium.*

Nature of Disturbance.	H ₂ CO ₃ Plasma.	BHCO ₃ Plasma.	H ₂ CO ₃ : BHCO ₃ Ratio.	pH Plasma.	Alkalinity of Plasma.	Results from:—
1. Uncompensated alkali excess	N +	++	—	+	+	1. Overdosing with bicarbonate 2. High intestinal and pyloric obstruction
2. Uncompensated CO ₂ deficit	—	N—	—	+	+	Overbreathing:— 1. Voluntary. 2. High altitudes 3. High temperature 4. Cardiac failure
3. Compensated alkali excess	+	+	N	N	N	Early stage of 1
4. Compensated CO ₂ deficit	—	—	N	N	N	Early stage of 2
5. Normal acid-base equilibrium	N	N	N	N	N	
6. Compensated CO ₂ excess	+	+	N	N	N	Early stage of 8. Emphysema
7. Compensated alkali deficit	—	—	N	N	N	Early stage of 9
8. Uncompensated CO ₂ excess	++	N+	+	—	—	1. Experimental breathing CO ₂ 2. Morphine poisoning
9. Uncompensated alkali deficit	N—	—	+	—	—	1. Abnormal production of acids as in diabetes 2. Retention of acid metabolism as in nephritis

N = Normal.
+ = Increased.

++ = More increased than +.
-- = More diminished than —.

TABLE II. *Chemical Changes in the Blood and Urine.*

Case No.	Date.	Hour.	Plasma.			Serum.			Blood.		Urine.					
			Bicar- bonate % c.c. of CO ₂ .	Chlorides % as NaCl.	Phos- phorus % as P.	Sodium % as Na.	Calcium % as Ca.	Total base as gramme equi- valent per litre.	Urea % as urea.	pH.	Ammonia in 100 c.c.	Titratable Acid in 100 c.c.	Chlorides % as NaCl.	Phos- phorus % as P.	Organic Acid in 100 c.c.	Urea % as urea.
1.	16.6.21	—	61	0.64	0.0057	—	—	—	0.141	5.4	8 c.c. N/10	11 c.c. N/10	—	0.033	—	—
	12.7.21	—	94	0.54	0.0074	0.32	—	—	0.150	7.8	—	—	—	0.024	—	—
	21.7.21	—	86	0.54	0.0078	—	—	—	0.138	7.	—	—	—	—	—	—
2.	23.2.22	3.30 p.m.	101 ²	0.53	—	0.38	0.010	—	0.130	—	—	—	—	—	—	—
3.	20.12.23	11 a.m.	7.6	0.295	0.0075	0.33	0.011	—	0.265	—	—	—	—	—	—	—
	21.12.23	11.30 p.m.	75	0.49	—	—	0.011	0.155	—	5.6	22 c.c. N/10	24 c.c. N/10	Trace	0.036	68 c.c. N/10	1.2
	21.12.23	11 a.m.	7.45	—	—	0.32	—	—	0.132	—	—	—	—	—	—	—
4.	29.1.24	11.30 a.m.	7.6	0.39	—	—	—	—	—	—	—	—	—	—	—	—
	30.1.24	1 p.m.	—	—	—	—	—	—	—	5.0	48 c.c. N/10	60 c.c. N/10	0.05	—	70 c.c. N/10	—
	2.2.24	10.30 a.m.	7.43	0.63	—	—	—	—	0.191	Acid	—	—	Trace	—	—	22
5.	13.2.24	3.30 p.m.	7.43	0.478	—	—	0.012	0.150	0.276	—	29 c.c. N/10	27 c.c. N/10	Trace	—	Lactic acid 0.020	1.56
															Amino acid N	8.6 c.c. N/10

Remarks.—Case I. Chronic nephritis. Large doses of sodium bicarbonate from 3.7.21 to 18.7.21.
Case II. Cholecystitis and acute gastric erosions. Overdosing with sodium bicarbonate.
Case III (11 a.m.). Carcinomatous obstruction of the pylorus.

(11.30 p.m.). Gastric tetany.
Case IV (11.30 a.m.). Acute dilatation of stomach and duodenum.

(1 p.m.). Empyema and pyaemia.
Case V. General peritonitis and ileus. Gangrenous appendicitis.

² This figure is probably too low. The amount of excess acid which it is necessary to add when large amounts of bicarbonate are present was not realized at this time.

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